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PSYCHOTHERAPEUTICS AND THE SCHIZOPHRENIC REACTION

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The concepts of schizophrenia and of psychotherapy are not so precisely formulated, or their significances so generally agreed upon, that a clinician can speak meaningfully, unless he identifies his position in regard to a number of principles which he considers to be fundamental to his understanding and use of a therapeutic technique or method. Although therapists may differ one from another in the degree of clarity of conceptualization and in the extent to which they feel committed to any system of ideas, they have opinions—sometimes unstated and often but dimly recognized—regarding all aspects of their professional (and other) living. Clearly perceived or not, their tasks are carried on with some consistency of reference to a particular philosophy. (This last term refers to a group of principles underlying a particular discipline—in this case, the general field of psychiatry, and more specifically, one aspect of it—the psychotherapeutics of the schizophrenic reaction.) I am of the opinion that it is useful for a therapist to recognize his philosophy, and to keep it readily available for recurrent consideration by himself and for presentation to others, there being improved prospects for its flourishing and undergoing useful change when exhibited to the often rigorous, but occasionally salubrious, climate of public opinion.

A therapeutic procedure may reflect ideas of the therapist regarding disease in general, and a variety of subjects which are, or which he considers to be, related in some manner to the sickness which he encounters. The way in which the treatment is applied will express not only his training and skill, but his attitudes toward himself and others. With certain notable exception, the principles of treatment will be an outgrowth or a manifestation of the physician's concept of the disturbed state, and thus logically, at least, will be suited to the therapeutic problem. That the basic concept from which principles are derived may be erroneous or inadequate emphasizes our need to view and review with care that which we profess, but does not signify that we should try to work without such concepts, or that we should necessarily fear becoming endeared to them, recognizing that with affection may come increase of determination and strength, but that the object of our regard very possibly may be expected to exhibit frailties and undergo a decline with the passing of time.

In reference to his professional labors a psychotherapist is more or less precise in his thinking about the following: (*a*) a workable definition of the disorder treated, (*b*) its clinical course, (*c*) its origins—the influence of early life events in its formation and development, the constitutional-hereditary factors, defects in metabolism and organic structure, and so on, (*d*) the relationship of the disorder to the family of the patient, and to the larger community culture, (*e*) its appearance in various age groups, (*f*) the psychologic manifestations

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and their significances, (*g*) the rationale of treatment and the complexities associated with the practice of therapy, (*h*) the meaning of the disorder in terms of common human experiences—in this instance isolation, nonrelatedness, loneliness, and death.

In what follows I shall summarize my views regarding the psychotherapy of schizophrenia and certain conceptions on which that treatment is based.

Man's Heritage and Psychiatric Disorder

In their work psychotherapists function in reference to some conception of the way in which the human personality comes into being. Such a schema is useful in the evaluation of the patient's behavior, his accounts of his early life, the possible relatedness of present and past events and the implications of his hereditary and bodily organization.

The *biologic heritage* of man is referred to as his genotype—a complex of potentialities marked by definite limits of development. The genes, transmitted from one generation to the next, are not the carriers of particular "characters" or "traits," but contain the potentials of patterns of behavior that are developed, expressed and to some extent modified by environmental influences. Man's great uniqueness lies not only in his ability to adapt to his surroundings, but in his use of symbols in language and thought, with the aid of which he may modify his behavior in terms of his past experience, and in response to constructs of the future—his foresight.

The term *constitution* does not refer to a fixed biologic condition destined to exist unaltered through the years of a person's life. The term describes a process of interaction between the inherited genetic potentialities and the environment in which they are given opportunity for expression.

Culture refers to that in the environment which is man-made. Having been invented by man, it is modified by him and transmitted to his descendents. Man forms his culture, but is influenced by, and to a considerable extent formed by that which he has created.

Man's heredity has three components: (*a*) the *genetic*—those potentials of development which have limits but are not completely unalterable, and depend to a considerable extent on their surroundings for their realization; (*b*) the influences of *intrauterine* existence—by which is implied studies suggestive of a considerable responsiveness of the fetus to the mother and her reactions to external stimuli; (*c*) the *cultural* heredity—created by man and to a remarkable extent creative of him. The terms *heredity* and *constitution* have a great latitude of meaning. It does not seem possible to interpret a pattern of behavior as a reflection of purely environmental or hereditary influences, these being greatly dependent upon each other for the degree and form of their expression.

Aside from those catastrophic physical deformities that interfere with the development of anything like adequate human performance, the assumption can be made that man's potential abilities are seldom fully developed or displayed, and that these capacities, given suitable encouragement, are adequate to meet the requirements of human life. That is, the schizophrenic patient, or a person adorned with some other label, can be regarded as someone who has very largely *learned* to be the kind of person that he is, and who very likely has capabilities somehow undeveloped through lack of necessary experience, or inhibited in expression by cultural influence. Although I am no great optimist about therapeutic performances of any kind, and have a certain grim respect for the tendency of unfortunate patterns of human behavior to persist, in considering any patient there comes to mind the observation of Thoreau to the effect that, "Man's capacities have never been measured."

The human can be considered as born with an orientation toward the fulfilment

of his capacities. Human behavior is seen both as a response to and as a reflection of the biologic and cultural environments. I do not think of man as being driven by forces fundamentally destructive to himself or his fellows, or engaged in a war with a culture created by him yet somehow unbecoming to him. The picture of man as strongly motivated toward realization of his potentials as a human suggests his culture as the continuing expression of his capabilities and needs and an impressive agent in the formation of his character. When certain features of the culture restrict and distort human performances, reducing creativity and efficiency, and in time are reflected in persistent alterations of the personality, the psychiatrist is presented with one of his therapeutic problems—the patient who displays in a most subtle and complex form the resultant of the acts of God and man.

To varying degrees the "symptoms" which our patients show reflect attempts of the organism to adapt itself to forces threatening to its effective functioning and the expression of its capabilities. In some instances these adaptive efforts are inadequate, or become excessive, and in themselves interfere with the healing process and growth. Of particular interest is man's remarkable ability to react, not only to threats in the present and in the immediate environment, but to symbols of events which threatened him in the past—dreams, memories and signs of earlier troublesome occurrences. Among those events are the interpersonal contacts which man experiences as disturbing to the concept of himself as referent to his concept of others. In other words, the human develops a considerable concern with a construct developed entirely in his dealings with his fellows—his self-esteem. In efforts to improve or maintain the equilibrium of this sensitive indication of his estimate of his relationship to others, he may elaborate the patterns of his behavior to such an extent that they become excessively complicated, and are inadequate to attain the goals toward which they are appropriately directed.

Mental illnesses may be regarded as varied forms of behavior developed by the human organism in response to cultural and other environmental influences (including alterations in the body's internal economy). The effect of such behavior may be that the person feels more adequate (one may speak instead of reduction of tension) and is thereby enabled to continue some form of more or less acceptable relatedness to others. The behavior which is manifested eventually to the degree that it is labeled "sick" serves various functions: (*a*) it reduces distress, although distressing in itself, (*b*) it expresses the pain experienced and (*c*) it helps in the maintenance of some form of contact with other humans. Illness is the persistent, recurrent patterns of behavior exhibited in interpersonal relationships and characterized by being inappropriate, destructive and unnecessarily complicated in terms of efficient performance in the social field in which they occur. Although such patterns tend to persist, they may alter in circumstances in which there is provision for more effective performance. Therapists are concerned with the discovery, understanding and use of such influential circumstances.

Comments on Some Early Life Experiences

Patterns of behavior reflect to a large degree previous experiences with significant people. Such people—sometimes poorly prepared, on occasion unwilling, and frequently with no clear awareness of their role—have the function of introducing and interpreting to the child the characteristics of the culture. From these teachers the child develops knowledge of events labeled "right" and "wrong," "significant" and "unimportant." Through them he forms a sense of values and develops a way of perceiving his world, which, barring somewhat unusual corrective circumstances, will remain to a considerable extent a part of him for the remainder of his

days. Having formed a concept of life, how it was, is and ought to be, with the guidance of those impressively important to him, he thereafter tends to distort his observations of events, people and things in such a way that this long established concept, experienced as an integral and valued part of the self, will not be disturbed.

In early life human behavior expresses attempts to satisfy various biologic necessities, such as the requirements for food, drink, rest and sleep. The human infant also develops a remarkable need for security in response to the tenderness and care given him by his mother and others intimately concerned with his welfare. In this earliest period of postnatal life there is formed an interaction between the infant and the mothering one, in which the needs of both may be expressed, elaborated and satisfied. In this relationship both participants increase their abilities to give and receive tenderness as well as other emotions. This exchange flourishes in a situation in which words are not yet used to convey meaning, and in which there is no clear distinction made by the infant (or, to an extent, by the mother) between the two of them as separate entities.

In these early months of his life the human infant is extraordinarily dependent upon those who care for him. In general he is cared for by a few people, often only one, from whom he receives food, physical care and his first experiences with the human personality and its emotional expressions. He cannot move about and must deal with that which is brought to him, be it food, anger, love, fear or hatred. He cannot run or turn to another person. He can only be where he is and sense the impact of humanity and his culture through this as yet unidentified other being.

Up to the present time there appears to be no convincing evidence that the young infant has any clear concept of himself or others as distinct entities. In response to certain tensions, such as hunger, he may cry, and at the reduction of tension he may sleep. The origins of such tensions or the modes of their relief are not clear to him, events being unrelated to one another in any causal or serial fashion. Life at that time is composed of momentary states, and is not marked by a past which in our culture is thought of as running into a present and on to a future. This early experience is not comprehensible to the infant in terms of himself, or of others separated from him, of time sequences, of purpose, or of relatedness of events. The details of the surrounding environment are not clear, but are prehended in a totality, or *Gestalt*, marked by a sentience which is the early step in the growth of meaning and emotion. In other words the world is not occupied by people, furniture, speech, emotions of anger or love, and so on. There is simply a wholeness which may exist while one feels comfort or discomfort. Experience has a "cosmic" quality in which details are undifferentiated, and in which time, events, people and feelings, all poorly defined and not clearly related to states of tension, flow together in a movement unconnected with that which has been, is, or will be.

The infant, not being clearly separated from others and being most intimately exposed to the mothering one, is greatly influenced by her attitudes as expressed, for example, in gesture, tone of voice, facial movements and ways of touching. The behavior of another (the complex of emotion and bodily movement) may be experienced by the infant as his own behavior; the extensions of his body and his self being ill defined.

During the first year of life this "cosmic" quality of experience alters. The infant develops an increasingly clear concept of himself and others. He becomes aware of a time sequence in the requirements of his body and in the social customs of his family. The early rudiments of past, present and future are presented to him, and some possible connec-

tions between events are observed and acted upon. Mother is no longer simply an extension of himself and people other than she take form to be comforting or otherwise.

The infant is empathically responsive to the attitudes of his mother (responding with tenseness to her tension), the communicative process being gestural as well as vocal. As skill in the use of language is gained an increase is seen in the preciseness of perception and the evaluation of interpersonal events. The child's need for security, developed in his relationships with others, has become a fundamental need which must be met. He is now dependent upon the opinions of others for his security, not just upon their behavior. In brief, he is on the way, for the remainder of his days, to being related to his fellows, with whose behavior his growth, actions and emotions are inextricably involved.

After the age of two there is a great expansion of the child's world, as he gains facility in speech, learns something of other children, and has increased contact with ideas contrasting to some extent with those expressed in his family. Later he learns something of competition, and cooperation with others, and in his early adolescence discovers the deep significances of friendship and the fundamentals of love. If all goes well his sexual interests find increasingly effective expression as his affection for his friend is extended to love for someone of the opposite sex.

What can be emphasized here is the concept that the potential for growth must be met at any one time by the appropriate opportunity for its expression. Without such opportunity growth will not occur in the usual fashion and a distortion of development will appear. Interferences with the growth process at any point, resulting from traumatic events or experiential lacks, lead to developmental defects which interfere with later adequate growth unless met by other corrective experiences. As an example, defects in learning important functions usually expressed in the juvenile era will interfere with the acquisition of fully adjustive behavior in preadolescence. The psychiatrist has interest in these phenomena because he is required to work with those who display the unfortunate results of earlier life events which have led to interferences in later learning.

When speaking of the "personality" I refer to the recurrent patterns of interpersonal situations in which the person becomes involved during the course of his living. Human behavior cannot be comprehended without reference to the multitude of social fields which have formed its background and characterize its present. In this sense the personality cannot be isolated from the social field —the complex of interpersonal relationships —in which it exists. The recurrent patterns of relationship or ways of dealing with others in their totality constitute what we speak of as personality. In this sense we are our behavior (although this may be too narrow a view).

The Phenomenon of Anxiety

At some time there enters into the life of the infant the tension of anxiety. This is an experience of discomfort in response to a similar tension in the mothering one, the transmission of feeling being empathic, or nonverbal. Before the experience of anxiety the infant's feelings of comfort depend on the meeting of his needs for food, warmth, sleep and bodily contact. As he develops a relatedness to others his need for their responsiveness increases in amount and complexity, and he becomes reactive to the emotion of his associates. Having no clear conception of himself or others, of time, or of the relatedness of events, the infant is peculiarly susceptible to anxiety in others.

In infancy anxiety is experienced as discomfort without clear reference to interpersonal events; comfort or discomfort exists, there being no recognition of people

or events as causative. As the sense of self and of others is elaborated the infant may associate his state of comfort with another person without evaluating the details of that other's behavior. Thus he may feel at ease with mother at one time, and ill at ease at another, there being a vague prehension of "comforting" or "discomforting" mothers who come and go without reason and whose actions cannot be controlled. In time these early crude concepts of one person experienced as different people give way to a picture of one person who has a variety of attributes.

The child learns that he feels ill at ease when mother is something called "tense", "nervous" or "anxious", or is disapproving of him. However, the very presence of anxiety interferes with the development of understanding of its nature. Anxiety interrupts the exercise of finely discriminating observations, with the result that the anxious person (in some ways like the infant) may act as if he were unaware of any connection between his unhappy state and the activities of other people. He may feel tense "without cause," or being discomposed in the presence of another, he may label him "bad," without being able to observe or to formulate accurately those aspects of the relationship which disturb him. In such instances the causation of the difficulty and methods for its relief do not receive adequate attention.

The infant is poorly equipped for the avoidance or reduction of the tension of anxiety. His anxiety is relieved adequately only by the reduction of that tension in those who care for him, and certain of his responses to anxiety, such as crying, increase the discomfort of others, and thus add to his own stress. Being unskilled in the use of many techniques of human living, the infant can only suffer when in contact with those who threaten his composure or if subjected to prolonged and severe anxiety he can withdraw into a state of apathy or detachment. From such early experience with anxiety may be formed an attitude of caution in regard to all human contacts, people being equated with the receiving of pain. Unless this concept is modified by more benign experience, future interpersonal relationships will be distorted and there will be interference with the adequate learning of various significant aspects of the culture.

The experience of anxiety as we know it in later life is one of marked discomfort. Elaborate ways of behavior, *i.e.*, defenses or security operations, are refined in the service of attenuating, distorting or avoiding the events which might give rise to it. When effective, these behavior patterns operate so automatically and rapidly, that for the most part we are exposed to fleeting contact with anxiety. We may feel angry, bored, contemptuous, depressed or envious, with no recognition that these commonplace feelings, often so readily "explained," serve as ways of increasing our security, having been carefully devised throughout the years to shield us from the distress of being anxious.

Anxiety, as used here, is a tension developed in relationship to others, is experienced in reference to others, and is a remarkable indicator of our sensitivity to those relationships. As he learns to be human man becomes inextricably involved with his kind and their common culture, and in doing so finds not only the opportunities for his own development but also refines that vulnerability to others which we call anxiety. The experience of anxiety is an expression of the complexity of our involvement with our fellow men, and is not resolved by withdrawal from them, finding sustenance for its continuance in the memories and dreams of our attachments to others. Withdrawal may lead to loneliness, a state less tolerable than that of anxiety. We may find ourselves torn by the fear of anxiety and loneliness, and unable to resolve the conflict between our need for the human relationships which provide the experiences required for our own further development and our

reluctance to risk feeling anxiety in those relationships. He who becomes schizophrenic knows well the great distress involved in attempts to resolve this enigma.

In brief, anxiety (as used in this somewhat limited way) is a peculiarly unpleasant experience, related to a remembered, present or anticipated decrease in self-esteem, and developed and experienced in human relationships. The phenomenon of anxiety is not easily identified, observed or altered for the following reasons: (*a*) its discomfort is not readily tolerated, (*b*) its origins may be obscure, (*c*) the events leading to its appearance may go unnoted, (*d*) its presence interferes with the observational, discriminatory, communicative and learning abilities of the sufferer, (*e*) there is usually no adequate method for dealing with it directly, and (*f*) its operation is obscured by the defenses set up in opposition to it.

Common to all psychiatric disorders is anxiety, often obscured by the behavior which we refer to as a "symptom." Symptoms are conceived here as patterns of behavior, learned to some extent from others who displayed them before the child, and in part developed as methods of attenuating and expressing the anxiety of an interpersonal relationship.

"Dissociation" and Schizophrenia

In the first year of life (and to some extent later) thought processes are considered to be diffuse and not clearly related to the events which they symbolize. Such processes, lacking in precision and dealing with the totality of a situation, are of value in gaining an initial prehension of experience, the situation or person being labeled as "good" or "bad" without reference to various nuances and refinements of meaning. Autistic, personal speech may become attached to these mental states, or they may not be associated with words, with the result in either case, that they are not readily communicated to others. As the use of language is refined, these less precise symbol operations are not satisfactory for dealing with other people, and tend to drop into disuse, fading from awareness.

Among these poorly formulated preconcepts are some which have been marked by severe anxiety, reflecting discomfort experienced in an important interpersonal relationship. The child, being remarkably dependent upon the maintenance of such a relationship (as with his mother), must cope with any threat to it, such as the disjunctive force of anxiety. For example, one may deal with an anxious experience by not attending to its details, by not formulating its significance, and thus letting it drop (as it were) from awareness.

Dissociation, then, refers to the failure to develop in awareness certain elements of interpersonal experience. Among these may be: (*a*) processes of thought associated with autistic ideas, not clearly expressed to others, and not adequate for meaningful communication; (*b*) concepts which are not required for dealing with the usual interpersonal relationships, and have been "forgotten"; (*c*) concepts of events and people that were not clearly comprehended, hence not available for association with other ideas, and did not become a part of the personality that was known, *i.e.*, that could be formulated and communicated to others; (*d*) experiences marked by anxiety and threatening to the maintenance of a significant human relationship.

The appearance in awareness of dissociated matters is disturbing, there being on such occasion a feeling of strangeness, as if that which came to mind was not a part of the self. If the dissociated material is a reflection of previous events connected with great anxiety, its reaching awareness is accompanied by a marked decrease in the sense of security, and the taking of action to dispel the troublesome ideas. The maintenance of ideas in dissociation requires a considerable degree of alertness to interpersonal events, there being a constant threat that the behavior of another may lead to a recall

of circumstances of the past concerned with the dissociation, in which case the disturbing ideas would gain awareness and anxiety increase. By continued alertness possible threats to the maintenance of the always precarious dynamic equilibrium are noted, avoided, "rationalized away" or inattended, their personal, painful implications not being developed. The maintenance of such attentiveness to the details of human behavior enables the organism to function, but requires a considerable expenditure of effort, and interferes with the development and expression of its potential.

In the schizophrenic reaction the person is no longer able to meet the requirements of the current situation, his anxiety increases, and the system of devices used to support an uncertain self-esteem fails to restrict awareness to those more precise referential processes which can be validated with others and characterize our more conventional thinking. With this extension of awareness, ill defined, poorly comprehended symbols of earlier life relationships are observed. Laden with anxiety, never having been comprehended clearly and marked by the total or cosmic quality of the interpersonal relationships of early life, such concepts seem strange, and may appear as awesome, frightful and terrifying generalities, the implications of which are obscure and difficult to communicate to others. Such an experience, as exhibited in the panic of schizophrenia, may be referred to as a "failure of dissociation."

One of the handicaps of the schizophrenic person is that certain important aspects of his relatedness to people are not readily available to his awareness and are not accessible as data in his dealings with others. His need for intimacy is threatened by the possibility that unguarded communication with someone will disturb the dissociation, and increase anxiety. Without the intimacy there is the danger of loneliness and the loss of opportunity for the satisfaction of his needs to exhibit tenderness and to communicate. In an effort to resolve this dilemma the person engages in activities designed to permit some degree of the necessary relatedness, and at the same time to maintain an always unstable system devised to assure some semblance of security and self-esteem. Considered from this point of view the behavior of patients may be understood as a remarkable demonstration of the skill required to carry on human relationships in a social field which is poorly understood, and is perceived for the most part as threatening and unreliable.

The Onset of Schizophrenia

Prior to the appearance of what is called psychotic behavior, the troubled person may use a variety of techniques to reduce the increasing distress which he experiences. The schizophrenic reaction is seen clearly after there has been a progressive failure, usually over years of time, of these efforts made to further a workable adjustment between the organism and the environment.

Long before a diagnosis of schizophrenia has been made, a young man, for example, may find that his contacts with other people carry with them an increasing threat of anxiety and humiliation. He may quietly and unobtrusively withdraw from such contacts, substituting for them simpler activities and fantasy, such as day dreaming, reading, lonely visits to the theater, sleep, and so on. Action involving relationships with others has become noticeably dangerous to him, and he turns to "thinking," in which relationships can be manipulated with some degree of assurance of personal satisfaction, and the outcome of events dependably predicted. Discomfort in interpersonal experience may be rationalized (explained away) or the significance of the events distorted or ignored, so that the impact of their painful implications is diminished.

From early infancy the use of sublimatory patterns has been developed; these consist of more complex activities and fantasy, in keeping with approved cultural standards,

substituted unconsciously for simpler, more directly goal-oriented behavior. Although these processes may enable the person to perform in a socially adequate manner, they become increasingly complex and they do not bring about a full satisfaction of needs.

The adolescent person is required to resolve a number of important issues: he must be able to collaborate with his associates, find a good friend, gain a satisfactory and approved form of sexual expression, reach some conclusions about marriage and the establishment of a home, gain independence outside of his family and enter a career. All of these activities involve participation and effective communication with other people, and the attendant danger of anxiety. Such defense as the quiet withdrawal, the use of sublimation and the obsessional substitutions are not adequate to deal with these increasingly complex social matters, and there may be observed evidences of failure to adjust and the recourse to less adequate forms of behavior in an effort to maintain the necessary contacts with others. Such behavior, often increasingly complex and no longer in conformity with social convention, includes the evasions, the unexplained "forgettings," rationalizations, transfers of blame, and various hypochondriacal physical incapacitations.

Our young man has been making use of increasingly complex and inefficient patterns of behavior in an effort (in the main, not clearly in awareness) to reduce his mounting anxiety, to maintain the dissociation of disturbing concepts, and to retain important human contacts. As these adjustive processes fail (often in adolescence under the pressure to resolve the need for lustful satisfaction and the fear of loneliness) his self-esteem declines further in the face of his increasingly apparent social inadequacies, and his field of awareness may include previously dissociated processes, symbols of earlier life experiences, poorly defined, not clearly related to the known past or present, and carrying with them an incomprehensible sense of urgency and terror.

With this failure of the adjustive efforts and the appearance of dissociative processes the schizophrenic state is evidenced in panic, a condition in which recent experience cannot be used effectively, in which perception is distorted, and in which frantic and poorly coordinated efforts are made to find a solution and to escape from the nightmarish disturbance.

The reaction of panic may be resolved in various ways: (*a*) through useful human contact the fear of others subsides, the necessity for dissociation is reduced, and the chances for forming more satisfactory interpersonal relationships increases, there being now the possibility of significant, profitable alteration in personality; (*b*) through further dissociation, in which case the person must move thereafter with increased caution, taking care to maintain the dissociation and to avoid a recurrence of the panic which he has come to dread; (*c*) by an attempt to use magical procedures for control of a poorly understood and continually threatening situation the "catatonic" state appears; (*d*) by withdrawal from much of the meaningful in human contact, and preoccupation with highly abstract symbolizations of interpersonal events and with bodily function—the "hebephrenic" state, and (*e*) through the massive transfer of blame and accompanying grandiosity of the "paranoid" solution.

The behavior which we finally call schizophrenic is a reflection of the development over years of time of increasingly inadequate ways of living with one's fellow humans. From this point of view the disturbing experiences of early life have not been well understood or adequately corrected, with the result that later experiences necessary for continued satisfactory development are not fully used and are viewed from a distorted point of view. Earlier inadequate methods of dealing with interpersonal relationships are not replaced, and the tech-

niques devised for the maintenance of some semblance of conformity with cultural requirements and some degree of self-esteem become unwieldy and ineffective in dealing with the necessities of adult living.

The behavior of the "disturbed" patient reflects attempts to deal with the admission into awareness of poorly comprehended symbols of previous interpersonal experiences. These concepts, unfamiliar, puzzling and terrifying, are expressive of such a degree of anxiety that panic is present or imminent, and their early definition and resolution are urgently required. The phenomena that appear in awareness reflect, in part, interpersonal relationships which occurred prior to the development of the concept of the self or of skill in the use of language, and, having been experienced in an atmosphere of great anxiety, were dissociated.

The Etiology of Schizophrenia

The therapist must work with some idea regarding the significance of the disorder which he is treating. It is possible to conceive of the schizophrenic process as a way of living which has been in part learned, and serves to enable the person to deal with his severe and chronic anxiety, as well as to maintain, at great expense in terms of personal efficiency, important relationships with others.

On the basis of the available evidence, I consider that the early life of the schizophrenic person is marked by unhappiness, emotional insecurity and severe anxiety, present before the child has developed adequate methods of dealing with those who cared for him, and before he is able to gain corrective help from people outside of the family circle. The social field of the family, from this point of view, is seen to be disordered and is reflected in the schizophrenic reaction.

The child is introduced to the complexities of his culture by his family, which is, in turn, an expression of that culture. His parents and other relatives transmit to him a social heritage; they interpret this heritage to him, influence his evaluations of it and mould his attitudes toward future teachers, so that he will accept more readily that which the family has designated as "good," eschewing that which they call "bad," and seeing life from the "family's point of view." These teachers of the culture are also the models for the child's behavior. For adequate learning these models should be clearly defined, should not be distorted by marked anxiety in their relationships with one another, and should provide security. The family life of the child who will become schizophrenic is marked by the presence of severe anxiety, lack of clarity in the parental roles, conflict between family members, and the presentation of a view of the culture which has been distorted in the service of the personal pathology of the elders. In such an environment the child develops an inadequate, biased concept of his culture, is handicapped in future learning, comes to fear participation in human relationships, and cultivates patterns of behavior whose primary purpose is to lessen anxiety and maintain the accepted concept of himself and family even at the expense of considerable misrepresentation of reality.

I picture the schizophrenic person as having had in his infancy a relationship of intense closeness with his mother, marked by his need for her, and in return her great need for him, reflecting her feelings of insecurity, inadequacy and loneliness. In this relationship, characterized by anxiety and mutual needs, the child experiences the fear that in human closeness he will be engulfed and will be unable to exist as an independent person. Such experience may be, in part, the background for the movements of approach and withdrawal, of acceptance and rejection, of promise and disappointment, which we observe in the treatment of the schizophrenic person.

It seems that much of what we observe in schizophrenic behavior can be comprehended as reflecting the troubled life within

the patient's family, and that we may continue to search with profit for more effective ways of studying these early life relationships. Whatever factors may at some later date be considered as fundamental in the etiology of the schizophrenic reaction, we cannot overlook the great importance of cultural and interpersonal influences in the moulding of human behavior.

General Comments on Psychotherapy

It is not necessary to speak of a particular type of psychotherapy, distinct in kind from all others, suited only to the schizophrenic person. There are certain fundamental concepts of psychotherapy which can be considered appropriate in dealing with patients however classified, and not out of place in many other interpersonal situations, professional or otherwise. Among these concepts are the following:

(1) A respect for another person whom we consider to be worthy of our esteem and upon whose privacy we would not obtrude without reason clearly directed toward his betterment.

(2) A willingness to listen to an account told by another without being threatened or seriously disconcerted by its containment of elements that are unfamiliar, that are at variance with our concepts of what is "right," or are seemingly irrational and more like the content of a dream than waking life.

(3) An ability to listen to another's point of view without feeling a great need to take action about it, to fashion it more in accordance with our preconceptions, or to distort it in the service of our own anxiety.

(4) An appreciation of the distress of anxiety and an alertness to its early manifestations in ourself, as well as in others.

(5) The exercise of such skill that anxiety will not be aroused, increased, or in special circumstances diminished, unless there is evidence that the alteration has some likelihood of benefiting the patient.

(6) Some concept of the human personality as a remarkably sensitive portrayal of the interaction of the organism with its environment.

(7) An ability to observe, and on occasion to participate in the social field of interaction between patient and therapist, seeing this as an area in which will be presented, in varying degrees of clarity, an account of previous human relationships and a statement regarding the significance of the current professional one.

(8) A realization that the behavior of participants in a social field, and their views of that field, will be distorted by their past experience and by the facts of their current interaction; that the presence of such distortions may go unnoted for long periods; and that the characteristics of such distortions must be identified and comprehended by both participants irrespective of any distress which such recognition may entail.

(9) An awareness of the obscurity of certain human motivations and the complexity of operations required to keep disturbing phenomena from entering awareness.

(10) A confidence, based on observation and experience, that given certain minimal opportunities, the human organism tends to move in the direction of more efficient and satisfying performances, and that the work of the therapist may be directed toward the identification and comprehension of interferences with that movement.

Psychotherapy is an interpersonal process concerned with the study of the behavior of the participants in a social field. The schizophrenic reaction has been elaborated as reflecting disorder in the social field of the family and as being manifest in interpersonal relationships. This is to say that the psychotherapeutic process and this psychiatric disorder may be looked upon as special instances of interpersonal phenomena. There is some reason to think that in the social field of the former can be displayed for study and intervention the difficulties of the latter.

Psychotherapy and Schizophrenia

I have outlined certain of my views relative to the schizophrenic reaction, in an attempt to show a meaningful connection between a concept of the disorder and the therapy which is used.

If one thinks of the characteristics of the person who has experienced a state of panic and thereafter comes for treatment, he can anticipate certain difficulties that will arise in the work, and will be able to predict the utility of various therapeutic techniques.

The schizophrenic person is shy and afraid, having experienced considerable distress in his relationships with other humans. In his contacts with others he feels handicapped because of his anxiety, and because of his defects in learning and experience. He is remarkably susceptible to the behavior of others, being at the mercy of anyone who can increase his anxiety. He is torn between the discomforts of anxiety and loneliness, and doubting the value of a human relationship and the usefulness of himself to any other person, he uses language and other behavior to keep himself at a safe distance from those who threaten him.

Such a person cannot communicate readily with others for various reasons, among which are the following: (*a*) he fears to risk ostracism by revealing himself as different, inadequate or sick; (*b*) at times dissociated processes disturb the organization of his awareness and cannot be verbalized; (*c*) autistic ideas cannot be explained easily to others; (*d*) he is ashamed of his defects, the origin of which is unknown to him; (*e*) he is fearful of revealing his anger and his hurt, because in so doing he might further estrange himself or destroy those he needs, and who may need him.

At times this person cannot understand himself and finds that his own behavior is not predictable, and that the meaning of much of what he experiences is unclear. He may feel evil, unwanted and generally inferior to his fellows. As his interpersonal security has been precarious for a long time his morale is not likely to be high, and it is quite probable that he has no great expectations of receiving help from, or even making sense with, a psychiatrist or anyone else. His experience has simply not been such as to lead him to entertain high hopes of what he can do with other people.

The problems of psychotherapy, and the use of appropriate techniques, will vary somewhat at different stages of the reaction, and no attempt will be made to consider in detail such variations at this time. The term schizophrenia, as here used, refers to a gross disturbance in the interpersonal field occurring during the period of chronologic adolescence or early adult life, and characterized by a course of events (the "onset") which is disrupted by a state of panic, eventually resolved in some fashion as briefly outlined above. In this condition the sufferer has passed through the periods of infancy, childhood, juvenality, and has met with the problems of pre- and early adolescence. He has learned something of the skills characteristic of each period although his experiences may have been markedly restricted or inappropriate, his learning inadequate, and his growing concept of himself and others increasingly skewed. His anxiety increased and clinical signs of failing adjustment becoming so extreme as to be classified as mental disorder even when viewed at a distance. His ineptness in the social field became more noticeable at the time when he was required to define himself more clearly as a person within his culture, and in doing so to become more profoundly related to others, as might be demonstrated by his selection of a career, expression of his sexual abilities, and gratification of his need for intimacy.

I have some interest in the possibility that the schizophrenic reaction may be but a point on a continuum of behavioral difficulties extending from infancy to adult life. In such case, we may observe that the child introduced into a social situation quite unsuited to the promotion of his relatedness

to others may become what was at one time called "marasmic," and die. Others, finding the environment anything but congenial (but consistent with life after the attainment of extraordinary distortions of behavior) develop that peculiarity of living known as "autism," whereas still others become schizophrenic children, who differ quite markedly from those who are not evidently schizophrenic until they have gained some experience in life beyond the eras of infancy and early childhood. It is my impression that the incidence of schizophrenia might be considerably increased were it not for experience with benign and literally life saving human relationships during childhood and later years.

In early adolescence, prior to the display of rapidly increasing anxiety, therapy may be concerned with the understanding of the formation and uses of the defensive structure of the personality, with the interferences with the forming of more intimate relationships, and with the provision of potentially useful interpersonal contacts. During the period of "onset" defects in organization of the personality are increasingly evident, and the patient engages in activities calculated to maintain a concept of himself and contact with others; this is the period of hypochondriacal impairment, withdrawal, fantasy, rationalization, elaboration of obsessional substitutions, and so on. At this time communication has not broken down, panic has not been experienced, and there is the opportunity for the formation of a relationship with a therapist, upon the basis of which anxiety may diminish, communication increase, the threat of sudden dissociation lessen, and the possibilities of learning from new experience increase.

When panic occurs the therapeutic problem is altered. In this state verbal communication is relatively ineffective, recent experience is not available for use in attempts to formulate ideas about present events and the use of foresight is minimal. In the presence of this nightmare, therapy is directed at the establishment of a relationship marked by clarity, dependability and security, with the primary goal of reestablishing greater definition of the sense of self.

When the state of panic has developed into other forms of behavior, such as catatonic, paranoid, hebephrenic, or social recovery, the therapeutic approach will be altered in accordance with the interferences of communication characteristic of the form in question. In all of these instances, therapy will be governed by the patient's previous experiences with programs of treatment. If he has been hospitalized for months or more, or has been treated by a variety of agents without noticeable or persistent benefit, his morale has very likely declined, in which case the problem is further complicated by the necessity of helping the patient rediscover some elements of hopefulness in a human relationship.

It seems to me that prospects for treatment may be improved by early recognition of the movement toward a schizophrenic reaction and by attempts to provide a nonobtrusive, mildly comprehending relationship long before the development of panic. The very acts related to identification and diagnosis of disorder may be beneficial, providing, as they frequently do, a benign human contact with accompanying reduction of both anxiety and loneliness.

Having devoted considerable space to comment on a variety of aspects of schizophrenia it is not appropriate to attempt herein any detailed account of psychotherapeutic operations, although the latter might be thought of as the theme of this presentation. It is useful for the therapist repeatedly to formulate and state his concept of the disorder treated, and to consider the possibilities of developing a therapeutic procedure which is in accordance with, and in some respects an expression of, the nature of the illness or social disorder. If the therapist of the schizophrenic patient has an understanding of the social field from which the reaction was derived and in which it finds

expression, he will discover ways of behaving in the interpersonal field occupied by himself and his patient that will illuminate obscurities without seriously disorganizing the field to the disadvantage of the anxious person. Details of the ways in which therapeutic actions are effected will vary with the characteristics of the social field. Precisely what is done will be a function of the personalities of those concerned, in this case patient and therapist.

There follows a brief exposition of certain problems which are commonly encountered in the psychotherapy of schizophrenic people, be they resident in a hospital or otherwise.

The Forming of a Relationship

Although the patient supposedly will benefit from his relationship with the therapist, his experience has led him to fear such involvement, with the result that he will often act in ways to disrupt or attenuate it. Into the treatment situation will be brought representations of the patient's earlier life, marked by anxiety and consequent distortion, the therapist often being the target of the anger, contempt, hatred and fear (and the great need for affection and understanding) symbolic of past experience and current need. In the presence of doubt, suspicion and misrepresentation, the physician attempting to form a communicative, increasingly secure relationship with his patient will be rebuffed frequently and will be tempted to give up his work, feeling on occasion that he, his patient, or both are unsuited to the task. If he considers carefully his personal qualities, he will usually find that he is in many ways not qualified to be a useful therapist. Having recognized his shortcomings and displaying some interest in their possible correction, he gets on with his work. He does not stop.

In response to his anxiety the patient will often seek to withdraw from contact with the doctor, by becoming evasive, sarcastic, mute, assaultive, and so on. The therapist will also experience anxiety, being at times inattentive, evasive, depressed or in other ways withdrawn. He may be of a mind to discontinue treatment. The therapist must accept his own anxiety as a frequent accompaniment of his work—a hazard, perhaps, but not a cause for dismay. He can only attempt to note the presence of his anxiety, the form taken by it, the pattern of its appearance, its possible origins and factors in the current social field which rouse it; he can make use of its movements as indicators of shifts in the therapeutic relationship and clues to further discovery of himself.

The success of psychotherapy is based upon the forming of a relationship, the creation and maintenance of a social field in which tension can be maintained at a level favorable to the development of meaningful communication. Therapy does not begin when communication is unobstructed, but is concerned with the nature of the obstructions; when these are identified and eliminated or reduced, formal treatment may cease, the patient being able to meet his needs through more adequate communication with others.

The therapist may concern himself at times with such matters as providing his patient with affection, tenderness or other support. I am of the opinion that tenderness is demonstrated by recognition of the need of another, and that an important need of the schizophrenic person is to be able to understand and to make himself understood. Although one may behave in various ways with patients, the common goal is the improvement of communication. As communication is facilitated and anxiety subsides, destructive activity on the part of the patient will diminish, as will the therapist's preoccupation with the feeling that he is required to do more than clearly comprehend. As understanding and the ability to express himself increases the patient will be able to find satisfaction for his

other needs, and the physician will not be required to provide for them.

The forming of a therapeutic relationship is complicated by the patient's fear of loss; what he gains he may lose, and he does not relish the pain of rejection or separation, finding it easier to manipulate memories than people. The therapist, recognizing this fear, will not be repulsed by his patient's apparent rejection, but will try again with a certain quiet persistence.

The Forms of Communication

As the experiences which are basic to the schizophrenic expression took place prior to the development of skill in the use of language or the formation of a clear concept of the self, they appear as diffuse and disturbing emotions, and tend to be expressed in action (of both the smooth and striated musculature) rather than in conventional speech. The therapist, therefore, is required to have a considerable sensitivity to the nonverbal components of communication, noting the messages conveyed by tone of voice, body movements, the method of dress, and so on. He must be knowledgeable about his own nonverbal expressiveness as well as that of others.

At times the communication will be of an empathic nature, by which is meant that the signs transmitting information will not be in the awareness of sender or receiver. In such instance the therapist may notice, for example, that he feels isolated and lonely, and may seek to explain his state and find its relief. He may eventually learn that his loneliness is in response to a multitude of subtle clues indicative of the patient's loneliness. Although the topic of loneliness may not have been discussed, the communicative process has been effective in that loneliness has now been experienced by the two; when the emotion is verbalized and the message recognized, much has been done to further communication and to alleviate the loneliness. The experiencing of emotions by the therapist often will be unpleasant (as in the above example) but every such experience must be evaluated in terms of its possibly representing a message from the patient.

"Closeness" in the Therapeutic Relationship

The word *close* means intimate and to "be in accord emotionally," but it also means shut in, confined, secluded, secret, hidden, oppressive, stifling and tenacious. The schizophrenic person often acts as if all of these meanings were involved in a relationship. In his work with the therapist he will experience aspects of his relationship with the mothering one, to whom he felt close without clearly being a person in his own right, and in whose presence he often felt intense anxiety. This experience of anxiety at a time when the concept of self was unclear is symbolized in later life as feelings of personal dissolution, "loss of the sense of self," lack of "control" and panic. In the developing relationship with the therapist, desirable as it is, there may be reexperienced the anxiety of infancy, the patient feeling that he is losing his identity, and that he may destroy (engulf), or be destroyed by (engulfed by) his therapist. At such times he may attempt to drive his therapist away, or terminate treatment, in efforts to preserve himself as a person, and also to maintain the integrity of the therapist. He fears that closeness and relatedness may lead to mutual loss of identity and destruction; the therapist who leaves is not destroyed, but can be retained in memory—which is considered to be better than total loss. Although there may be much talk of hatred and fears of killing and being killed, these terms on occasion may be conventional ways of referring to the recurrence in awareness of the infantile anxiety referent to a sense of mutual engulfment. The therapeutic benefit is derived from the reliving of this experience, the growing realization that neither patient nor therapist will be destroyed, and the clear identification of both

participants as distinct and independent people.

Sometimes it appears that a patient cannot tolerate any form of "closeness" or "relatedness," retreating or attacking in situations which from our point of view are benign. Thus it is sometimes said that he who is schizophrenic cannot abide love or intimacy, which state of affairs does not make good sense if the patient recognizes the situation as one marked by affection and serious concern for him. In the presence of such withdrawal it is useful to observe the therapeutic relationship for defects which may have been overlooked. Such characteristics as the following may be noted.

(1) Important aspects of the relationship are unclear, and the patient is disturbed by the obscurity, moving away from its possible implications.

(2) Some aspect of the therapist's personality (not in the awareness of the therapist) is experienced by the patient as threatening.

(3) The therapist is hostile toward the patient, but is unaware of this sentiment or attempts to conceal it.

(4) The therapist's behavior is benign in terms of his experience, but in terms of the patient's culture and experience is not acceptable.

(5) The patient may exhibit malevolent behavior when he desires affection (that is, having experienced rejection and hurt in supposedly loving contacts, he does not ask for love directly, but acts as if he had been rejected); not recognizing the patient's "hostility" as the distorted expression of the patient's request for tenderness, the therapist may feel rebuffed and reject the patient. In this case both patient and therapist may think that they have confirmed the patient's inability to tolerate "warmth."

(6) The patient may fear that the doctor comes close only to spy on awful secrets, or that he is ignorant of the presence of such secrets. In either case the patient fears that his physician will be disgusted, and will retreat, leaving the patient to loneliness.

It is entirely probable that the schizophrenic person can profit from respectful, loving experiences with another person. Because of his early poor fortune he tends to run or attack before he can identify an experience as benign. The therapist can only refuse to be pushed away, and attempt to identify not only the patient's distortions of the current scene, but those aspects of it which are quite realistically troublesome.

The Patient's Fear of Being "Used"

The patient often fears that he will be used for the satisfaction of the therapist's needs, a repetition of such experiences with the parent. In a number of instances I have noted that the parent (usually the mother) had some such need for the infant as follows: (*a*) to satisfy loneliness; (*b*) to repair or substitute for current interpersonal lacks, such as the loss of marital love; (*c*) to fulfil prestige needs; (*d*) to serve as a buffer against a growing sense of loss of personal identity, as in increasing maternal anxiety; (*e*) to use the infant as a symbol of a parent; being peculiarly responsive and susceptible to parental manipulation, the infant (and young child) may be used as both child and mother, these roles being marked by great emotional intensity and obscurity.

The patient who has experienced such relatedness will be at times quite effective in "mothering" the therapist, and also may misinterpret the therapist's actions as being directed toward the finding, rather than the giving, of support. It is useful for the physician to be aware of his needs and to have means for their satisfaction outside of the therapeutic situation.

The therapist will satisfy certain of his needs to some extent through his patient. Although psychotherapy is quite simply work, one may take pleasure in it and derive much satisfaction from the relationship with the patient. On occasion a patient may notice and respond to his therapist's need

for reassurance, for example, and in doing this recognize that the physician is not invulnerable to human ailment, and discover the satisfaction of being able to give as well as to receive. The point here is not a "use" of the patient for the physician's neurotic necessities, but a growing recognition by the participants of the reciprocal nature of a human relationship, in which needs may be recognized openly without fear that such recognition will be hurtful or even require action.

In the course of treatment the doctor and patient may each discover a need for the other in which both may act to perpetuate the relationship. Such needs are not cause for distress, but reflect the intensity and attachment developed over months, or more, of time. The great discovery for the patient is that his therapist can recognize and accept these mutual needs, and can continue to help him (the patient) grow and become more independent. In brief, unlike the parent, the therapist can have great regard for his patient, and can take pleasure in his leaving the treatment situation to establish relationships and find satisfactions elsewhere. In this instance love takes on a new meaning. It is tolerant of growth and separation.

Reactions of the Therapist

The therapist will experience varied and intense emotions in the treatment of the schizophrenic patient.

(1) He will become intensely related to his patient and may on occasion feel "dangerously involved," being disturbed by the awareness of his own emotions.

(2) Dissociated material expressed by the patient may seem unfamiliar, incomprehensible and disturbing, and may provoke "uncanny" feelings in himself, indications of experiences not yet in awareness. Such phenomena may be so unpleasant that the therapist will attempt to ignore them or "explain them away" to the disadvantage of treatment.

(3) The patient will be skillful in noting aspects of the therapist's personality which reflect such tendencies as to control, to be anxious, to be hostile or to be dependent, and may comment on these to the therapist's considerable discomfort.

(4) The therapist will be cast in many roles, the shift from one to another often being rapid and confusing.

(5) The patient's doubt of the value of a human relationship may lead the therapist to question his own worth, and he then may experience depression and discouragement.

(6) At times the therapist will sense in himself emotions seemingly inappropriate to his position; experiencing, for example, hatred, contempt, anger, fear or lustful feelings. In such case he can only look for the source of the emotions, determine if they reflect similar experiences of his patient, make no effort to deny them when observed by his patient, and continue with the work.

The psychotherapist is well advised to undertake a personal analysis with a competent therapist and to present his own therapeutic work to the scrutiny of experienced colleagues. Even with such preparation the therapist will feel strong emotion in the course of doing therapy, and will at times be anxious and insecure. It will be useful for him to consult with colleagues regarding various of his experiences, and on occasion he may freely acknowledge his own anxiety or other emotion to his patient, attempting to discover in the immediacy of the treatment situation the causes of the disturbance.

One of the great satisfactions in the practice of psychotherapy is found in the continued personal growth of the therapist. In the work with each patient one discovers more about himself. At times such discoveries are painful, and one may feel that he is unsuited for the task and should seek other means of livelihood. But the therapist recovers, and sees that the process of psychotherapy involves learning and growth, in which both participants discover some-

thing of themselves and of each other, and in which the growth of one involves the growth of the other.

The Therapeutic Process

In conclusion, there is presented an outline of what may be considered to be essential aspects of treatment. If the following tasks are accomplished I have some confidence in the patient's being able to live without recurrence of further schizophrenic disorder.

(1) A relationship with the therapist is developed in which positive and negative feelings can be experienced and expressed, on some occasions by both participants, without disruption of the social field.

(2) Dissociated material is expressed in the presence of the therapist, without there being a necessity to understand or interpret all, or much, of it. (As dissociated matters are expressed, autistic ideas and poorly comprehended symbols of previous experiences are available for association with better understood and more communicable concepts; the necessity for the alertness and the defensive structure to maintain the dissociation is reduced, and the patient is enabled to take greater advantage of new learning experiences.)

(3) The therapist is used as a model, and as someone who interprets the culture, in a fashion less distorted than that of the earlier teachers (the parents). (Having used the therapist as a model and figure of identification, the increasingly secure patient turns to other people for further teaching and identification.)

(4) The therapeutic relationship is at times marked by a quality of reality, that is, the situation is not always a representation of life; it is life, in which anger, grief and other emotions are experienced as immediate and directly concerned with the participants. In this way the symbols of the past are brought into the present, as it were, and dealt with in their full strength.

(5) The important relationships of the patient's earlier life are reexperienced with the therapist, the attendant distortions of perception in the interpersonal field being identified and corrected.

(6) By repeated reviews of the life history the patient gains a clear concept of the social field of the family, and of the relationship of the family to the culture; he has some idea of how he came to be the person that he is.

(7) Important experiences which were missed or not adequately dealt with in earlier developmental periods are identified and opportunities found for correcting these deficits by participation in appropriate situations.

(8) Learning defects, arising from the interference of anxiety or other causes, are corrected.

(9) Affectionate feelings between patient and therapist are recognized, as preliminary to the patient's expressing them towards others.

(10) The process of separation from the therapeutic situation is understood and looked upon as an inevitable accompaniment of growth.

(11) The patient is able to make an appropriate evaluation of important relatives, being able to accept them, hold his own with them, and be independent of them without needing to deny them or isolate himself from them in response to anxiety.

In this review of an approach to the psychotherapy of schizophrenic people, an effort has been made to show some connection between a concept of the disorder and the therapeutic method. Much more could be said about the concept and the method. The psychotherapy of schizophrenic patients as outlined here will not in itself dispose of the "schizophrenia problem." But in this work one can learn a good deal about human living, and in the course of doing that will at times be of service to some troubled, remarkable and potentially productive people. He will discover something of the strengths and weaknesses of himself as a therapeutic instrument, and perhaps will come to a greater realization of the extraordinary in-

terplay between the human organism and its environment.

The fundamental requirement of doing psychotherapy with a schizophrenic patient is to arrange matters so that you can meet with one until he has recovered from the schizophrenic reaction and attained some approximation of good mental health. To do so may take time and very considerable personal effort, and is no way to preserve a constant state of peace of mind. One cannot properly write or speculate about the schizophrenic reaction without having spent time with those who manifest it. Sometimes we have so little personal contact with people who are patients that what we think and say about them refers not to them, but only to some stereotype of what they seem to be. In such case the patients are not human or real; they are only things called "patients" or "schizophrenics." Before any usful psychotherapy can be done the therapist and the patient must meet each other as one person to another, the stereotypes having fallen behind. The following quotation from G. K. Chesterton (writing about G. B. Shaw) seems peculiarly appropriate to this concept of stereotype.

"At least one reason why Englishmen cannot understand Mr. Shaw is that Englishmen have never taken the trouble to understand Irishmen. They will sometimes be generous to Ireland.... They will speak *to* Ireland; they will speak *for* Ireland; but they will *not hear* Ireland speak. All the real amiability which most Englishmen undoubtedly feel towards Irishmen is lavished upon a class of Irishmen which unfortunately does not exist."

ANNOTATED REFERENCES

The literature cited, including items published during 1956 and the first half of 1957, relate to certain topics of interest to the psychotherapist.[2]

[2] A noteworthy omission is of philosophical writings of interest to the physician who puzzles about the implications of his work for the more general questions of the relatedness of man to his fellows and to his universe. The inclusion of such material would go beyond the scope of this article.

The articles are listed under the following headings:

(1) Schizophrenia and the organic substrate
(2) General studies of schizophrenia
(3) Concepts of the genesis of schizophrenia
(4) The family of the schizophrenic patient
(5) Culture and schizophrenia
(6) Schizophrenia and children
(7) Communication and schizophrenia
(8) Psychologic theory
(9) Social therapy
(10) Psychotherapy and the schizophrenic reaction
(11) Special aspects of psychotherapy
(12) Isolation, malignancy and death.

As an introduction to each of these sections there appears a brief comment on its general theses, and in some instances special reference to certain papers that appeared especially informative or useful to me in light of my particular interests.

(1) *Schizophrenia and the Organic Substrate*

(*a*) Endocrine studies
(*b*) Physiologic changes
(*c*) Neurologic factors

These few articles do not reflect adequately the large amount of work that has been reported on the biochemical, neurologic and physiologic studies of schizophrenic patients. These papers are included to suggest that the psychotherapist is well advised to be aware of this work and its implications for the growing understanding of the concept of schizophrenia.

Although trained in schools of medicine, many psychiatrists who devote the major portion of their time to the practice of psychotherapy are not well qualified to evaluate the technical procedures now used in the sciences often referred to as basic, or to interpret with satisfaction a variety of statistical studies. On occasion the therapist may feel awed, if not overcome, at viewing the large amount of data which is presented about the schizophrenic patient, and may feel discouraged at his own inadequacy in

reaching any proper comprehension of the material. In such case it is well for him to consider his patient who is ill and needs care; and to consider himself as one who cannot rightly permit his awe to turn him away from serving the sick as best he may. He may feel comforted, if he requires such, by the thought that the psychotherapeutic procedure, despite its defects, has been shown to be useful in the treatment of schizophrenic patients, and that the favorable results reflect growth of the personality and not its further restriction.

Although I have spoken of the "schizophrenic reaction," and consider schizophrenia to be a response of the organism to life events in which the behavioral patterns are very largely a reflection of interpersonal experiences in a particular culture, there are most certainly other opinions as to the essential nature of this condition.

For example: "I would say first that the biological, clinical, and psychological evidence justifies the belief that the various types of insanity are true disease entities or groups of entities." (Ralph W. Gerard, "The Organic Position on Etiology," in *Integrating the Approaches to Mental Disease*, Paul B. Hoeber, Inc., New York, 1957). He says further: "... I would be inclined myself to agree with Pierre Janet who said, 'The chemist will solve dementia praecox.'"

It is my opinion that the chemist, or for that matter, the psychologist, psychiatrist, or anyone else, is not going to solve the problem of human living, in that any complete understanding of it will be obtained. At this point I am being quite personal; "full understanding" and "solution" of aspects of human living often mean control of living, and I am not delighted at the thought that man might be "completely" controlled —even "for his own good."

In the course of prolonged intensive psychotherapy with schizophrenic patients I have been greatly impressed by the multiplicity, and often the severity, of bodily reactions, including changes in weight, recurrent diarrhea, cardiac arrhythmias, transient neurologic symptoms (and signs), vomiting, dermatologic changes and pain. There is a remarkable responsiveness of the organism during treatment. It would be of considerable interest to study physiologic-chemical changes in the schizophrenic during the course of psychotherapy extending over several years of time. It is possible that in this way we would learn more of the organism's reaction to stress and to alterations in the communicative process.

An interesting review of this field is reported by M. D. Altschule in *Bodily Physiology in Mental and Emotional Disorders*, Grune & Stratton, Inc., New York, 1953.

1. Arieti, S. The possibility of psychosomatic involvement of the central nervous system in schizophrenia. J. Nerv. & Ment. Dis., **123**: 324–333, 1956.
2. Batt, J. C., Kay, W. W., Reiss, M. and Sands, D. E. The endocrine concomitants of schizophrenia. J. Ment. Sc., **103**: 240–256, 1957.
3. Davidson, G. M. Schizophrenia. A survey of theory and practice. J. Nerv. & Ment. Dis., **123**: 149–161, 1956.
4. Fabing, H. D. Trends in biological research in schizophrenia. J. Nerv. & Ment. Dis., **124**: 1–7, 1956.
5. Grossman, H. J. and Greenberg, N. H. Psychosomatic differentiation in infancy. I. Autonomic activity in the newborn. Psychosom. Med., **19**: 293–306, 1957.
6. Horwitt, M. K. Fact and artifact in the biology of schizophrenia. Science, **124**: 429, 1956.
7. Parfitt, D. N. The neurology of schizophrenia. J. Ment. Sc., **102**: 671–718, 1956.

(2) *General Studies of Schizophrenia*

(*a*) Observations of patients on hospital wards
(*b*) Course of the disorder
(*c*) Classification
(*d*) Symptoms

The treatment of the patient may occur in a hospital setting, while the patient lives in his parental home, while he is working and living apart from relatives. In any case the environment in which the patient has his current existence cannot be overlooked with impunity while psychotherapy is in progress.

The papers listed here report observations of groups of patients labeled schizophrenic and treated in clinic or hospital settings. It is useful for the therapist who works with few patients and becomes remarkably familiar with their personalities (usually discovering that his "schizophrenic patient" soon becomes a person) to note the appearance of such patients as described by those who see them in greater numbers and who record the course of their living over long periods of time.

In these reports the following observations were very striking.

(1) The patient in the hospital is frightened and terribly alone in a threatening world, and inclined to withdraw from needed human contacts in an effort to reduce his terror.

(2) What we see as "schizophrenic deterioration" is contributed to by hospital monotony and social isolation.

(3) What the patient says and does is potentially comprehensible as symbolic expressions of interpersonal relationships.

(4) As the understanding of a patient increases, his isolation tends to diminish.

(5) Patients who are "alone in the world," without interested relatives or friends have the poorest prognosis in terms of leaving the hospital.

It is noteworthy that not many articles were concerned with nosology, symptomatology or the onset of schizophrenia. Some aspects of symptom formation are discussed in articles listed under "Psychological Theory." (*See* Szasz, T. S. *Pain and Pleasure.* Basic Books, Inc., New York, 1957, Ch. 8.)

1. Cameron, J. L., Freeman, T. and McGhie, A. Clinical observations on chronic schizophrenia. Psychiatry, **19:** 271–281, 1956.
2. Cohen, B. D. Motivation and performance in schizophrenia. J. Abnorm. & Soc. Psychol., **52:** 186–190, 1956.
3. Crandell, A., Zubin, J., Mettler, F. A. and Kugelmass, N. "Mobility" in chronic schizophrenia with special regard to psychosurgery. Psychiatric Quart., **30:** 96–113, 1956.
4. Diethelm, O. A contribution to the course of schizophrenic illness. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
5. Errara, P. A sixteen-year follow-up of schizophrenic patients seen in an outpatient clinic. A. M. A. Arch. Neurol. & Psychiat., **78:** 84–88, 1957.
6. Fish, F. J. The classification of schizophrenia. The views of Kleist and his co-workers. J. Ment. Sc., **103:** 443–463, 1957.
7. Israel, R. H. and Johnson, N. A. Discharge and readmission rates in 4254 consecutive first admissions of schizophrenia. Am. J. Psychiat., **112:** 903–909, 1956.
8. Kretschmer, E. The multidimensional structure of schizophrenias in connection with their therapy. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
9. Morgan, N. C. and Johnson, N. A. Failures in psychiatry. The chronic hospital patient. Am. J. Psychiat., **113:** 824–830, 1957.
10. Segal, H. Depression in the schizophrenic. Internat. J. Psycho-analysis, **37:** 339–343, 1956.

(3) *Concepts of the Genesis of Schizophrenia*

(*a*) Psychologic trauma
(*b*) Heredity
(*c*) "Toxic" changes

It seems quite possible that there is considerable individual variation in the reaction to stress and that some people may tolerate better, or adjust differently to interpersonal affronts that in others lead to marked withdrawal, dissociation and eventually schizophrenic behavior. The schizophrenic patients about whom I have been writing managed to reach at least chronological adolescence before exhibiting psychotic behavior. They had no persistent intellectual defect, and did not seem to be markedly different from other people, except that they were lonely, did not entertain a very high opinion of themselves or others and had no great enthusiasm about possible profit to be gained in further interpersonal adventurings. The person who becomes schizophrenic seemingly has had a very complicated time indeed in his early life, complicated by obscure contacts with anxious and insecure parents or guardians, and has had very good reason to be wary of his fellows. To the present I have had no personal knowledge of anyone who

became schizophrenic after growing up in an environment characterized by clarity of interpersonal experience, security, a low level of anxiety, and occupied by adults who were able to present to him a view of the culture not grossly distorted by their own personal necessities. I suggest that people who become schizophrenic (as the term has been used here) are biologically adequate to survive profitably in the culture if they are spared the burden of a number of severely handicapping interpersonal experiences.

Of considerable interest is the appearance of a schizophrenic reaction in one child, while others in the same family may not become psychotic. The family environment is not the same for all, and is experienced differently by each member. It would be profitable to study the social organization of the family in terms of each child, considering the possibility that that organization alters with the addition of each new member, and that parental behavior is not a constant, but may vary strikingly in response to the needs of the parent and the child.

The references listed do not represent all written recently on the several topics noted, and are suggestive of further reading.

The following quotation regarding etiology is taken from the book, *Integrating the Approaches to Mental Disease*, edited by H. D. Kruse.

"The concept of etiology as embraced by modern psychiatry differs from the simple cause and effect system of traditional medicine. It subscribes to a 'field theory' hypothesis in which the interactions and transactions of multiple factors eventuate in degrees of health or sickness . . ." (National Advisory Mental Health Council, Evaluation in Mental Health, 1955.)

1. Beckett, P. G. S., Robinson, D. B., Frazier, S. H., Steinhilber, R. M., Duncan, G. M., Estes, H. R., Litin, E. M., Grattan, R. T., Lorton, W. L., Williams, G. E. and Johnson, A. M. The significance of exogenous traumata in the genesis of schizophrenia. Psychiatry, **19**: 137–142, 1956.
2. Bettelheim, B. Schizophrenia as a reaction to extreme situations. Am. J. Orthopsychiat., **26**: 507–518, 1956.
3. Bender, L. and Hitchman, I. L. A longitudinal study of ninety schizophrenic women. J. Nerv. & Ment. Dis., **124**: 337–345, 1956.
4. Jackson, D. D. A note on the importance of trauma in the genesis of schizophrenia. Psychiatry, **20**: 181–184, 1957.
5. Jung, C. G. Schizophrenia. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
6. Kallman, F. J. and Roth, B. Genetic aspects of preadolescent schizophrenia. Am. J. Psychiat., **112**: 599–606, 1956.
7. Kruse, H. D. (editor): *Integrating the Approaches to Mental Disease*. Paul B. Hoeber, Inc., New York, 1957.
8. Money, J. *The Psychologic Study of Man*. Charles C Thomas, Publisher, Springfield, Ill., 1957, Ch. 8.
9. Muller, H. J. Genetic principles in human populations. Am. J. Psychiat., **113**: 481–491, 1956.
10. Solomon, R. and Bliss, E. L. Simultaneous occurrence of schizophrenia in identical twins. Am. J. Psychiat., **112**: 912–915, 1956.
11. Wolman, B. B. Explorations in latent schizophrenia. Am. J. Psychotherapy, **11**: 560–588, 1957.

(4) *The Family of the Schizophrenic Patient*

(*a*) Studies of the parents of patients
(*b*) The family as a social unit

There has been increasing attention paid to the study of the social field in which the schizophrenic patient spent his youth. At the same time these data are gathered regarding hereditary factors, it is being observed that an extrabiologic inheritance of cultural experiences is of considerable importance in the understanding of the personality and its disorders. The patient has been studied as a biologic organism carrying some sort of constitutional or hereditary defect, and as a psychologic entity whose behavior reflected internalized struggles between his impulses and his environment. As interest in the social environment of the patient grew, studies were made of the personalities of one or both parents, of the siblings, and others, emphasis being placed on the characteristics of the relationship between the patient and some other member of his family.

The family may be considered to be a social field in which the behavior of one member of the field reflects and influences to a considerable extent the actions of others. To my way of thinking, this concept has great value in the treatment of the schizophrenic patient. The patient cannot alter without change occurring in the other members of the social field in which he is involved. For example, relatives may seem to oppose a patient's becoming "better" or more independent, and remove him from treatment at a time of therapeutic advance. Such behavior can be comprehended more adequately when seen as an attempt by the relative to maintain a constancy of the field, and can be dealt with by the provision of help to the relative so that he can make those changes in himself which will permit his or her child to grow further.

If the schizophrenic reaction is looked upon as being in part an expression of the social field, one is in the position of needing to study and identify the disorder in that field preliminary to attempting to alleviate the trouble. Gathering the data about such a field is not a simple matter, the informants often being unable to give more than a distorted or fragmentary account of what has occurred. The life within the family, and as experienced by a child in it, may be strikingly different from that life as reported by the parents (or child), by siblings or by others in the community. The relationships leading to the production of dissociation and chronic anxiety are subtle, carried on privately, and usually difficult to observe or to report. However, in the study of this field (the family) may come many data to help us understand more about the variants of human behavior, not only the common patterns labeled "substitution," "projection," "repression," and so on, but the multiplicity of variants which makes each of us differ from his fellows.

The therapist working in a social field occupied by his patient and himself sees acted out in that field symbolic representations of the interpersonal relationships that exist within the family. The behavior in the therapeutic field, including the reactions of the therapist, is another method for gathering data about previous social fields in which the patient has lived.

The therapist will learn much about his schizophrenic patient by reading the articles listed here, many of which include excellent bibliographies.

1. Bowen, M. Family participation in schizophrenia. Paper presented at the meeting of the American Psychiatric Association, 1957.
2. Galvin, J. Mothers of schizophrenics. J. Nerv. & Ment. Dis., **123:** 568–570, 1956.
3. Kohn, M. L. and Clausen, J. A. Parental authority behavior and schizophrenia. Am. J. Orthopsychiatry, **26:** 297–313, 1956.
4. Lidz, T., Parker, B. and Cornelison, A. The role of the father in the family environment of the schizophrenic patient. Am. J. Psychiat., **113:** 126–132, 1956.
5. Lidz, T., Cornelison, M. S. S., Fleck, S. and Terry, D. The intrafamilial environment of schizophrenic patients. II. Marital schism and marital skew. Am. J. Psychiat., **114:** 241–248, 1957.
6. Lidz, T., Fleck, S., Cornelison, A. and Terry, D. The intrafamilial environment of the schizophrenic patient. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
7. Limentoni, D. Symbiotic identification in schizophrenia. Psychiatry, **19:** 231–236, 1956.
8. Litin, E. M., Giffen, M. E. and Johnson, A. M. Parental influence in unusual sexual behavior in children. Psychoanalyt. Quart., **25:** 37–55, 1956.
9. Johnson, A. M. and Robinson, D. B. The sexual deviant (sexual psychopath)—causes, treatment, and prevention. J. A. M. A., **164:** 1559–65, 1957.
10. Prout, C. T. and White, M. A. The schizophrenic's sibling. J. Nerv. & Ment. Dis., **123:** 162–170, 1956.
11. Tec, L. Vicissitudes in guidance of parents of schizophrenic children. J. Nerv. & Ment. Dis., **124:** 233–238, 1956.
12. Wahl, C. W. Some antecedent factors in the family histories of 568 male schizophrenics of the United States Navy. Am. J. Psychiat., **113:** 201–210, 1956.
13. Wolman, B. B. Explorations in latent schizophrenia. Am. J. Psychotherapy, **11:** 560–588, 1957.
14. Wynne, L. The family environment of schizophrenic patients. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.

(5) *Culture and Schizophrenia*

(*a*) The relationships of the schizophrenic reaction to the culture in which it arises and is manifest

It has been reported that the incidence of schizophrenia does not vary greatly from one culture to another, which may suggest the presence of a basic biologic defect. It is noteworthy that careful studies of family organization and of interpersonal relationships within the family have not been made in various cultures, nor is much known about differences and similarities in such interpersonal experience. Are such phenomena as dissociation and withdrawal related more to inborn traits, for example, or are they common human techniques for dealing with failures in communication, great anxiety or other problems?

The schizophrenic reaction, being strikingly manifest and occurring in a variety of cultures, serves as a useful focus for the study of human development in differing circumstances.

Unless the psychotherapist knows a good deal about the culture in which his patient developed, communication will be unduly complicated. Behavior cannot be understood with any adequacy without reference to the culture in which it occurs and which it reflects. Much difficulty in comprehending what the patient has to say may arise from the patient's difficulty in describing something he was too young or too anxious to grasp well, or from the therapist's lack of experience with aspects of living known to his patient, or inability to picture the life being described.

A knowledge of the culture does not "explain" all of human behavior, but without that knowledge any explanation is likely to be deficient.

Again, this is not a complete bibliography. I recommend the book, *Culture, Psychiatry, and Human Values*, by M. K. Opler; it presents an excellent summary of the work done in this field.

1. Abel, T. M. Cultural patterns as they affect psychotherapeutic procedures. Am. J. Psychotherapy, **10**: 728, 1956.
2. Opler, M. K. *Culture, Psychiatry, and Human Values*. Charles C Thomas, Publisher, Springfield, Ill., 1956.
3. Opler, M. K. Cultural anthropology and social psychiatry. Am. J. Psychiat., **113**: 302-311, 1956.
4. Redlich, F. C. Social class, culture, and schizophrenia. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
5. Singer, J. L. and Opler, M. K. Contrasting patterns of fantasy and motility in Irish and Italian schizophrenics. J. Abnorm. & Social Psychol., **53**: 42-47, 1956.

(6) *Schizophrenia and Children*

(*a*) Childhood schizophrenia
(*b*) Autistic children
(*c*) Psychotherapy and psychotic reactions in childhood

Although the psychotherapy of schizophrenic children has not been discussed, the therapist will find much in the literature on this subject that will be useful to him in furthering his understanding of the schizophrenic process, working with the relatives of his patients and developing therapeutic techniques. The relationship between the marasmic child, the autistic child, the schizophrenic child and the adolescent or adult schizophrenic person is certainly not clear. Studies which are made of the social fields in which these disorders occur will be of great interest.

The article by Eisenberg presents an excellent review of studies of autistic children. The articles by Szurek and Berlin discuss problems of etiology, symptomatology, psychodynamics and therapy, and there is an excellent bibliography in that entitled "Psychotic episodes and psychotic maldevelopment."

Although in the therapy of adolescent and young adult schizophrenics the patients will probably establish a life for themselves away from the parental home (thus following the accepted cultural pattern in the United States) there is much to be learned from reports of therapy carried on with the

parents and the child. The success or failure of treatment with an adult schizophrenic patient may depend upon the giving of proper understanding and support to the relative (or others) to whom the patient is intensely related, avoiding in this way what may become a disruption of a long integrated social field in such a fashion as to be detrimental to the interests of the patient.

1. Bender, L. Schizophrenia in childhood. Its recognition, description, and treatment. Am. J. Orthopsychiat., **26:** 499–506, 1956.
2. Bender, Lauretta and Grugett, A. E. A study of certain epidemiological factors in a group of children with childhood schizophrenia. Am. J. Orthopsychiatry, **26:** 131–145, 1956.
3. Eisenberg, L. The autistic child in adolescence. Am. J. Psychiat., **112:** 607–612, 1956.
4. Eisenberg, L. and Kanner, L. Early infantile autism. Am. J. Orthopsychiat, **26:** 556–566, 1956.
5. Michael, C. M., Morris, D. P. and Soroker, E. Follow-up studies of shy, withdrawn children. II. Relative incidence of schizophrenia. Am. J. Orthopsychiat., **27:** 331–337, 1957.
6. Spotnitz, H., Nagelberg, L. and Feldman, Y. Ego reinforcement in the schizophrenic child. Am. J. Orthopsychiat., **26:** 146–164, 1956.
7. Szurek, S. A. and Berlin, I. N. Elements of psychotherapeutics with the schizophrenic child and his parents. Psychiatry, **19:** 1–9, 1956.
8. Szurek, S. A. Psychotic episodes and psychotic maldevelopment. Am. J. Orthopsychiat., **26:** 519–543, 1956.
9. Wilcox, D. E. Observations of speech disturbances in childhood schizophrenia. Dis. Nerv. System, **17:** 20–23, 1956.

(7) *Communication and Schizophrenia*

(*a*) Communication theory
(*b*) Nonverbal communication
(*c*) Linguistic studies

The psychotherapist is concerned at all times with the problem of discovering what his patient means by his words and actions, and in transmitting meaning to his patient. A guarded, shy, suspicious person is not likely to speak freely, and the presence of autistic ideas or dissociated processes further interferes with the gaining of clarity, words often being quite inadequate to express such experience. Meaning in the interview is transmitted through words, by vocal variations (tone, pitch, and so on), by nonverbal gestures and on occasion by writings, paintings, and other means. The schizophrenic patient has difficulty in the use of conventional modes of communication, and the psychotherapeutic process is very much involved in the identification and correction of disruptions or defects in communication.

The schizophrenic reaction has been looked upon as a reflection of communication disturbances occurring at an early age without later adequate correction. The schizophrenic person, having little hope of making sense in a satisfactory way to other people, is easily discouraged and withdraws, substituting action for words and breaking off communication. It is of primary importance that the therapist, unable though he may be to understand much of what occurs in the interaction with his patient, does not withdraw, become discouraged or make elaborate verbal statements concerning matters which he does not comprehend. The therapist works in a complex field in which a small amount of what goes on may be clear, a larger amount may have only possible symbolic significance, and a much greater amount is obscure or simply not understood at all. If therapy is to progress, the therapist must operate on the assumption that meaning about a number of useful concepts can be established—and he must be persistent.

The book by Ruesch, *Disturbed Communication*, will be of considerable interest to the therapist. The following is a quotation from the paper presented by Ruesch at Zurich in September, 1957.

"... From all the evidence available today the human reply is one of the most significant therapeutic agents operative in the psychological or socal therapies of schizophrenia. When a person—be it doctor, nurse, relative, or friend—responds unequivocally to the intention of the patient and the patient is given an opportunity

to respond in return, the foundations on which recovery can take place have been laid."

The study of the communicative process through linguistic analysis of recorded interviews and through the observation of cinematic recordings is a laborious and technical procedure, but one of great interest in identifying and mapping the detailed structures of the therapeutic situation. I recommend that the therapist make a recording of some of his treatment sessions, listening to these alone and in the company of colleagues. The experience will be both disconcerting and illuminating.

By listing these articles it is suggested that the therapist may usefully turn his attention to work being done in communication theory.

1. Bateson, G., Jackson, D., Haley, J. and Weakland, J. Toward a communication theory of schizophrenia. Behavioral Sc., **1**: 251–264, 1956.
2. Goldfarb, W., Braunstein, M. A., and Lorge, I. A study of speech patterns in a group of schizophrenic children. Am. J. Orthopsychiat., **26**: 544–555, 1956.
3. Gordon, J. E. The efficacy of two kinds of therapist verbal behavior in lifting repression. Ph.D. Thesis, Pennsylvania State University, Department of Psychology, 1956, unpublished.
4. Mazzanti, V. E. and Bessell, H. Communication through the latent language. Am. J. Psychotherapy, **10**: 250–260, 1956.
5. McQuown, N. A. Linguistic transcription and specification of psychiatric interview materials. Psychiatry, **20**: 79–86, 1957.
6. Meerloo, J. A. M. Human camouflage and identification with the environment. Psychosom. Med., **19**: 89–98, 1957.
7. Pittenger, R. E. and Smith, H. L., Jr. Some contributions of linguistics to psychiatry. Psychiatry, **20**: 61–78, 1957.
8. Ruesch, J. *Disturbed Communication.* W. W. Norton & Company, Inc., New York, 1957.
9. Ruesch, J. Remarks about communication in schizophrenia. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.

(8) *Psychologic Theory*

(*a*) Ego formation and structure
(*b*) Ego defects and function
(*c*) Studies of consciousness, dreams, perception, speech, thought
(*d*) Denial, introjection, repression, depersonalization, body image
(*e*) Dynamics of various behavior patterns
(*f*) Anxiety

The therapist has some sort of theoretical conception of his work. When so moved he will tell you how he views the development of the personality, what he thinks of "mechanisms of defense" or of "security operations," the movements and origins of anxiety, and so on. In the psychotherapy of schizophrenic patients much behavior is displayed which gives clues to the formation and structure of the personality. In recent years a very considerable literature has been built up concerning the psychology of the ego, and the references listed here are selections from the writings published in the past 18 months.

The book by Fletcher, *Instinct in Man*, is a valuable review of theories of instinct.

The work of Burnham on misperception is of great interest to the therapist of the schizophrenic patient, as is that of Beres on ego deviation. The article by Erikson is a detailed and excellent account of his concept of ego identity and supplies a good bibliography. Fisher's experimental studies on dreams throw light not only on the nature of dreams, but on problems of perception, and the phenomenon of selective inattention. The book by Szasz, *Pain and Pleasure*, presents some useful theoretical formulations about such phenomena as depersonalization.

The therapist is well advised to attempt a definition of his theoretical position, to recognize its usefulness and its limitations, and to consider the possibilities for its useful alteration. He need not be irrevocably bound to a theory, but he should not deceive himself by thinking that he works without a theory; the theory accompanies action, and should be in awareness; otherwise its operation will be covert and the chances for its improvement minimal.

1. Arieti, S. The double methodology in the study of personality and its disorders. Am. J. Psychotherapy, **11**: 532–547, 1957.
2. Beres, D. Ego deviation and the concept of schizophrenia. Psychoanalyt. Study Child, **11**: 164–235, 1956.
3. Berne, E. Ego states in psychotherapy. Am. J. Psychiat., **11**: 293–309, 1957.
4. Bion, W. R. Development of schizophrenic thought. Internat. J. Psycho-analysis, **37**: 344–346, 1956.
5. Boyer, L. B. On maternal overstimulation and ego defects. Psychoanalyt. Study Child, **11**: 236–256, 1956.
6. Burnham, D. L. Misperception of other persons in schizophrenia. A structural view of restitution processes, reality representation, and perception. Psychiatry, **19**: 283–303, 1956.
7. Bychowski, G. General aspects and implications of introjection. Psychoanalyt. Quart., **25**: 530–548, 1956.
8. Bychowski G. The ego and the introjects. Psychoanalyt. Quart., **25**: 11–36, 1956.
9. Cantril, H. Perception and interpersonal relations. Am. J. Psychiat., **114**: 119–126, 1957.
10. Collier, R. M.: Consciousness as a regulatory field. A theory of psychopathology. Psychol. Rev., **63**: 360–369, 1956.
11. Erikson, E. H.: The problem of ego identity. J. Am. Psychoanalyt. A., **4**: 56–121, 1956.
12. Fisher, C. Dreams, images, and perception. J. Am. Psychoanalyt. A., **4**: 5–48, 1956.
13. Fisher, C. Construction of dreams and images. J. Am. Psychoanalyt. A., **5**: 5–60, 1957.
14. Fletcher, R. *Instinct in Man*. International Universities Press, Inc., New York, 1957.
15. Freeman, T., McGhie, A. and Cameron, J. L. The state of the ego in chronic schizophrenia. Brit. J. M. Psychol., **30**: 9–18, 1957.
16. de la Garza, L. O. and Worchel, P. Time and space orentation in schizophrenics. J. Abnorm. & Social Psychol., **52**: 191, 1956.
17. Grant, V. W. Paranoid dynamics. A case study. Am. J. Psychiat., **113**: 143–149, 1956.
18. Grauer, D. Some misconceptions of Federn's ego psychology. J. Am. Psychoanalyt. A., **5**: 282–292, 1957.
19. Jacobson, E. Denial and repression. J. Am. Psychoanalyt. A., **5**: 61–92, 1957.
20. Johnson, A. M., Giffin, M. E., Watson, E. J. and Beckett, P. G. S. Observations on ego functions in schizophrenia. Psychiatry, **19**: 143–148, 1956.
21. Kubie, L. S. Influence of symbolic processes on the role of instincts in human behavior. Psychosom. Med., **18**: 189–208, 1956.
22. Leavitt, H. C. Generic relations between anxiety and fear. Psychoanalyt. Rev., **44**: 65–72, 1957.
23. Levin, M. Wit and schizophrenic thinking. Am. J. Psychiat., **113**: 917–923, 1957.
24. Macalpine, I. and Hunter, R. A. *Schizophrenia 1677—A Psychiatric Study of an Illustrated Autobiographical Record of Demoniacal Possession*. William Dawson & Sons, Ltd., London, 1956, 197 pp.
25. MacDonald, J. M. and Galvin, J. A. U. Experimental psychotic states. Am. J. Psychiat., **112**: 970–976, 1956.
26. Masserman, J. H. Evolution *vs.* "Revolution" in Psychiatry. A Biodynamic Interpretation. Behavioral Sc., **2**: 89–100, 1957.
27. Modell, A. H. Some recent psychoanalytic theories of schizophrenia. Psychoanalyt. Rev., **43**: 181–194, 1956.
28. Perry, J. W. A Jungian formulation of schizophrenia. Am. J. Psychotherapy, **10**: 54–65, 1956.
29. Reid, J. R. and Finesinger, J. E. Defenses. their nature and function. Am. J. Psychiat., **112**: 1015–1020, 1956.
30. Scher, J. M. Perception. Equivalence, avoidance, and intrusion in schizophrenia. A. M. A. Arch. Neurol. & Psychiat., **77**: 210–217, 1957.
31. Searles, H. F. The psychodynamics of vengefulness. Psychiatry, **19**: 31–40, 1956.
32. Stevenson, I. Is the human personality more plastic in infancy and childhood? Am. J. Psychiat., **114**: 152–161, 1957.
33. Szasz, T. S. *Pain and Pleasure. A Study of Bodily Feelings*. Basic Books, Inc., New York, 1957.
34. Szasz, T. S. A contribution to the psychology of schizophrenia. A. M. A. Arch Neurol. & Psychiat., **77**: 420–436, 1957.
35. Szasz, T. S. A contribution to the psychology of bodily feelings. Psychoanalyt. Quart., **26**: 25–49, 1957.
36. Szasz, T. S. The psychology of bodily feelings in schizophrenia. Psychosom. Med., **19**: 11–16, 1957.
37. Thornton, N. Some notes on schizoid personality. Psychoanalyt. Rev., **43**: 220–227, 1956.
38. Weckowicz, T. E. Size constancy in schizophrenic patients. J. Ment. Sc., **103**: 475–486, 1957.

(9) *Social Therapy*

(*a*) Use of psychiatric hospital as therapeutic agent
(*b*) Relationship of hospital to community
(*c*) Use of community resources as aids to therapy
(*d*) Characteristics of hospital

In discussing psychotherapeutic procedures emphasis may be placed on the exchanges between physician and patient, there being little attention paid to other relationships which may be significant in

promoting or retarding the patient's progress. In this presentation there has been no consideration of the treatment process carried on in a hospital, although these remarks are intended to be relevant to the therapy of patients both in and out of a hospital.

In the hospital the patient is in contact with other patients and with a variety of staff members, some of whom may become of great importance to him in constructive, and sometimes destructive, ways. The therapist will be concerned with the nature of the situation in which the patient lives, and often will find that collaboration with others (administrative physician, aide, nurse, relative, social worker) will dispel needless obscurities and reduce some of the interferences with improvement of the patient's performances.

The concept of the hospital as a "therapeutic community" is growing, and may reflect to some extent the rapid increase of population in this country with the accompanying increased emphasis on cooperation, controlled competition and group enterprise. The point is that the therapist is justified in an interest in the details of the current environment within which the patient is living, recognizing the power of the milieu as a force influencing behavior. In this regard E. E. Krapf states, "Even the most individual psychotherapy is to a certain extent a social therapy."

The psychotherapist is in part concerned with the identification and increasing comprehension of previous life events which have played a part in moulding the patient's behavior. He cannot ignore later events, including those in the recent past and predictions of others to come, which also may have influenced (or may influence) patterns of behavior which continue to be modifiable, although long established.

The articles listed are suggestive of writing in this field, and include some interesting descriptions of efforts being made to further hospital and community collaboration in the rehabilitation of patients. The list is deficient in that there are not included a greater number of reports by nurses, and some by social workers. *The Patient and the Mental Hospital* will be of interest to any therapist working with hospitalized patients.

1. Baker, A. A. and Thorpe, J. G. Deteriorated psychotic patients. Their treatment and its assessment. J. Ment. Sc., **102**: 780–789, 1956.
2. Freudenberg, R. K., Bennet, D. H. and May, A. R. The relative importance of physical and community methods in the treatment of schizophrenia. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
3. Goffman, E. On the characteristics of total institutions. Proceedings of the symposium on Preventive and Social Psychiatry, Walter Reed Army Institute of Research, Washington, D. C., April 15–17, 1957.
4. Hurst, L. C. The unlocking of wards in mental hospitals. Am. J. Psychiat., **114**: 306–308, 1957.
5. Jones, M. The concept of a therapeutic community. Am. J. Psychiat., **112**: 647–650, 1956.
6. Krapf, E. E. The social therapy of schizophrenia. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
7. Lewis, A. Restoring the schizophrenic to the community. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
8. MacDonald, J. and Daniels, M. L. The psychiatric ward as a therapeutic community. J. Nerv. & Ment. Dis., **124**: 148–155, 1956.
9. Myers, J. M. The role of the administrative psychiatrist in intensive psychotherapy in a mental hospital. Am. J. Psychiat., **113**: 71–74, 1956.
10. Will, Gwen T. Psychiatric nursing administration and its implication for patient care. In *The Patient and the Mental Hospital*, The Free Press, Glencoe, Ill., 1957.

(10) *Psychotherapy and the Schizophrenic Reaction*

(*a*) Individual psychotherapy

Articles concerned with group and multiple therapy have not been included, although reports of such work may be useful in the illumination of certain obscure aspects of individual psychotherapy. I have listed the book by Hill, published earlier

than the other articles and books, because of its obvious relevance.

The use of electronarcosis or other forms of physical therapy as an adjunct to psychotherapy is discussed in three articles (3, 9, 10). The procedure is recommended by the authors as a method of shortening hospitalization and aiding in the development of a therapeutic relationship. Psychotherapy is concerned with those factors which favor or interfere with the freedom of communication in the therapeutic situation and elsewhere. It is in the identification and comprehension of such factors that the essence of the therapeutic procedure is found. If an interference with communication is dealt with by the use of, for example, electric methods to alter the functioning of the cerebral cortex, the advantages to be gained from overcoming such a block by interpersonal means are lost, or altered. So far, I have not seen reports which lead me to favor the use of such methods to alter tensions in the interpersonal field.

It is noteworthy that this listing does not include articles on the use of ataractic drugs as adjuncts to psychotherapy. To date, there seem to be no accounts of prolonged, intensive psychotherapy accompanied by the use of such agents. It will be of interest to learn how the use of such drugs may affect the development of the doctor-patient relationship, the manifestation of transference distortions, the expression of emotion, and other relevant phenomena. At present I am concerned with psychotherapy as a procedure used to further a more adequate integration of the personality and a more satisfying expression of abilities; the drugs and convulsive agents mentioned have not been demonstrated, in my opinion, as helpful in reaching these goals.

The literature contains relatively few reports of the details of the course of psychotherapy or of the personal experiences and involvements of the therapist. Studies of sound and visual recordings of psychotherapeutic sessions with schizophrenic patients should yield information of value in this area.

1. Abse, W. The psychotherapy of schizophrenia. Paper (to be published) presented at the Annual Meeting of the Medical Society of St. Elizabeth's Hospital, 1957.
2. Azina, H. and Wittkower, E. D. Gratification of basic needs in treatment of schizophrenics. Psychiatry, **10**: 121–129, 1956.
3. Bogen-Tietz, E. and Jordan, J. H. Rapid treatment of the psychotic patient integrating electronarcosis and psychoanalytic psychotherapy. Am. J. Psychiat., **113**: 68–72, 1957.
4. Cowden, R. C. The psychophysiology of schizophrenia. Am. J. Psychiat., **113**: 709–716, 1957.
5. Fromm-Reichmann, F. Intensive psychoanalytically oriented psychotherapy of schizophrenics. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.
6. Hayward, M. L. Problems in the psychotherapy of schizophrenia. Pennsylvania M. J., **59**: 470–474, 1956.
7. Hayward, M. L. and Taylor, J. E. A schizophrenic patient describes the action of intensive psychotherapy. Psychiat. Quart., **30**: 211–248, 1956.
8. Hill, L. B. *Psychotherapeutic Intervention in Schizophrenia*. The University of Chicago Press, 1955.
9. Hill, L. B. and Patton, J. D. When physical therapy (shock) facilitates psychotherapy. Am. J. Psychiat., **113**: 60–65, 1956.
10. Kalenowsky, L. B. Problems of psychotherapy and transference in shock treatments and psychosurgery. Psychosom. Med., **18**: 399–403, 1956.
11. Kolb, L. C. Psychotherapeutic evaluation and its implications. Psychiat. Quart., **30**: 579–597, 1956.
12. Livermore, J. B. A schizophrenic child reviews her own treatment. Am. J. Orthopsychiat., **26**: 365–375, 1956.
13. Rifkin, A. H. *Schizophrenia in Psychoanalytic Office Practice*. Grune & Stratton, Inc., New York, 1957.
14. Sechehaye, M. *A New Psychotherapy in Schizophrenia*. Grune & Stratton, Inc., New York, 1956.
15. Silverman, S. and Cutler, R. E. Further observations on supervised psychotherapy of schizophrenia. Am. J. Psychotherapy, **11**: 262–276, 1957.
16. Sullivan, H. S. *Clinical Studies in Psychiatry*. W. W. Norton & Co., Inc., New York, 1956.
17. Waldron, F. E. Outpatient treatment of schizophrenia. Internat. J. Social Psychiat., **2**: 39–43, 1956.
18. Whitehorn, J. C. and Betz, B. J. A comparison of psychotherapeutic relationships between physicians and schizophrenic patients when

insulin is combined with psychotherapy and when psychotherapy is used alone. Am. J. Psychiat., **133:** 901–910, 1957.
19. Wilkins, Ann. The meaning of external control to a schizophrenic adolescent. Bull. Menninger Cl., **21:** 140–152, 1957.
20. Zilboorg, G. The problem of ambulatory schizophrenias. Am. J. Psychiat., **113:** 519–525, 1956.
21. Zilboorg, G. Ambulatory treatment of schizophrenics. Paper presented at the International Congress for Psychiatry, Zurich, Switzerland, 1957.

(11) *Special Aspects of Psychotherapy*

(*a*) Concept of psychotherapy
(*b*) Methods of study of therapeutic field
(*c*) Problems of transference, or aspects of doctor-patient relationship
(*d*) Group therapy.

In this group are listed articles concerned with the general concept of psychotherapy and with certain aspects of this procedure, such as difficulties arising in the doctor-patient relationship. There are a variety of subjects listed, but all are related to the interests of the therapist who works with schizophrenic patients, if he thinks of his work as having special problems intimately associated with the general field of psychotherapy.

1. Alexander, F. *Psychoanalysis and Psychotherapy*. W. W. Norton & Co., Inc., New York, 1956.
2. Binswanger, L. Existential analysis and psychotherapy. In *Progress in Psychotherapy* (edited by F. Fromm-Reichmann and J. L. Moreno). Grune & Stratton, Inc., New York, 1956, pp. 144–148.
3. Collier, R. M. A definition of treatment. Am. J. Psychotherapy, **11:** 45–55, 1957.
4. Di Mascio, A., Boyd, R. W. and Greenblatt, M. Physiological correlates of tension and antagonism during psychotherapy. Psychosom. Med., **19:** 99–104, 1957.
5. Dreikurs, R. Adlerian psychotherapy. In *Progress in Psychotherapy* (edited by F. Fromm-Reichmann and J. L. Moreno). Grune & Stratton, Inc., New York, 1956, pp. 111–118.
6. Ehrenwald, J. Telepathy. Concepts, criteria, and consequences. Psychiat. Quart., **30:** 425–445, 1956.
7. Ellenberger, H. The ancestry of dynamic psychotherapy. Bull. Menninger Cl., **20:** 288–299, 1956.
8. Farrar, C. B. Psychotherapy. Am. J. Psychiat., **113:** 865–870, 1957.
9. Fromm-Reichmann, F. and Moreno, J. L., editors. *Progress in Psychotherapy*. Grune & Stratton, Inc., New York, 1956.
10. Glad, D. D. An operational conception of psychotherapy. Psychiatry, **19:** 371–382, 1956.
11. Gordon, J. E. Leading and following psychotherapeutic techniques with hypnotically induced repression and hostility. J. Abnormal & Social Psychol., **54:** 405–410, 1957.
12. Hora, T. Beyond countertransference. Am. J. Psychotherapy, **10:** 18–23, 1956.
13. Kline, N. S. Criteria for psychiatric improvement. Psychiat. Quart., **31:** 31–40, 1957.
14. Kris, E. The recovery of childhood memories in psychoanalysis. Psychoanalyt. Study Child, **11:** 54–88, 1956.
15. Lessel, S. Psychotherapy and ataraxics. Some observations on combined psychotherapy and chlorpromazine therapy. Am. J. Psychotherapy, **10:** 448–466, 1956.
16. Malmo, R. B., Boag, T. J., Smith, A. A. Physiological study of personal interaction. Psychosom. Med., **19:** 105–119, 1957.
17. Mendelsohn, R. M., Yates, J. W. and Peterson, L. The experiential aspect of psychotherapy. Am. J. Psychotherapy, **11:** 254–261, 1957.
18. Reik, L. E. The historical foundation of psychotherapy in schizophrenia. Am. J. Psychotherapy, **10:** 241–249, 1956.
19. Rogers, C. R. Client-centered therapy. A current view. In *Progress in Psychotherapy* (edited by F. Fromm-Reichmann and J. L. Moreno). Grune & Stratton, Inc., New York, 1956, pp. 199–209.
20. Rosenbaum, M., Friedlander, J. and Kaplan, S. M. Evaluation of results of psychotherapy. Psychosom. Med., **18:** 113–132, 1956.
21. Semon, R. G. and Goldstein, N. The effectiveness of group psychotherapy with chronic schizophrenic patients and an evaluation of different therapeutic methods. J. Consulting Psychol., **21:** 317–322, 1957.
22. Shotin, L., Freed, E. K., Rockmore, L. and Funk, F. C. Somato-psychotherapeutic approach to long-term schizophrenic patients. J. Nerv. & Ment. Dis., **123:** 141–148, 1956.
23. Spitz, R. A. Countertransference. J. Am. Psychoanalyt. A., **4:** 256–265, 1956.
24. Szasz, T. S. On the experiences of the analyst in the psychoanalytic situation. J. Am. Psychoanalyt. A., **4:** 197–223, 1956.
25. Szasz, T. A. A critical analysis of the fundamental concepts of psychical research. Psychiat. Quart., **31:** 96–108, 1957.
26. Szasz, T. S. On the theory of psychoanalytic treatment. Internat. J. Psycho-Analysis, **38:** 166–182, 1957.
27. Tower, L. E. Countertransference. J. Am. Psychoanalyt. A., **4:** 224–255, 1956.

28. WHEELIS, A. The vocational hazards of psychoanalysis. Internat. J. Psycho-Analysis, **37**: 171–184, 1956.
29. WHITEHORN, J. C. Understanding psychotherapy. In *Progress in Psychotherapy* (edited by F. Fromm-Reichmann and J. L. Moreno). Grune & Stratton, Inc., New York, 1956.
30. WHEELWRIGHT, J. Jung's psychological concepts. In *Progress in Psychotherapy* (edited by F. Fromm-Reichmann and J. L. Moreno). Grune & Stratton, Inc., New York, 1956, pp. 127–135.
31. WOLSTEIN, B. Transference and immediate experience. Am. J. Psychotherapy, **11**: 277–292, 1957.

(12) *Isolation, Malignancy and Death*

(*a*) Studies of the personalities of those suffering from neoplastic disorders

(*b*) Reaction of human beings to isolation and feelings of being unrelated to their fellows

The therapist who works with schizophrenic patients will become involved in the phenomena of isolation and loneliness and will discover that these are unpleasant states to experience and exceedingly difficult to report to others. There is not much written in the psychiatric literature on the subject of loneliness; he who experiences this in any degree has, in the main, little to say about it, and what he does say seems to be only distantly related to the experience.

In discussing the social field of the family the concept has been developed that alteration in the personality (expressed in behavior) of one member of such a field requires alterations in other members, leading to the formation of a new field integration. In some instances such alteration may involve gross emotional disturbance in some member of the field (other than the patient, for example), eventuating in death in some instances. It is with this idea in mind that the schizophrenic reaction has been sometimes referred to as a potentially fatal disorder; the patient or some one else may die, the integrity of the earlier field organization being maintained by the employment of memories of the departed. By this is implied that the memory of the absent member is substituted for his reality, and things remain "as they were."

It has been my opinion on occasion that the occurrence of death in certain people (patient or his relative) has been in some way a consequence of a feeling of isolation, it being felt that there is no prospect of gaining a relationship with any other human being. I am suggesting the possibility that the feeling of total unrelatedness is incompatible with life in the human being. In theraputic work we are concerned with relatedness and may note that in isolation, and in loneliness, some degree of relatedness is maintained by fantasy and life continued, although behavior grossly altered (as in hebephrenic withdrawal).

Of the man who has become tabu (and thus unrelated) Cannon wrote as follows.

"The organization of his social life has collapsed, and no longer a member of a group, he is alone and isolated. The disowned man is in a situation from which the only escape is by death ... He becomes what the attitude of his fellow tribesmen wills him to be ... No more fiendish punishment could be devised, were such a thing physically possible, than that one should be turned loose in society and remain absolutely unnoticed by all the members thereof."

Evans speaks of the unrelatedness of some patients who develop cancer, "... the basic problem is that of being driven back into himself."

With the above ideas in mind these articles have been listed because each appears to have some bearing on the concept of relatedness. The psychotherapist observes isolation, loneliness, defects in relatedness, in some cases malignancy, and on occasion death. An interesting connection may exist between malignant and fatal developments and the state of being unrelated.

1. AZINA, H. AND CRAMER, F. C. Effects of partial perceptual isolation in mentally disturbed individuals. Dis. Nerv. System, **17**: 117–122, 1956.
2. BRODY, S. Psychological factors associated with disseminated lupus erythematosus and effects

of cortisone and ACTH. Psychiatric Quart., **30**: 44–60, 1956.

3. Brosin, H. W. The primary process and psychosis. Behavioral Sc., **2**: 62–67, 1957.
4. Buber, M. Distance and relation. Psychiatry, **20**: 97–104, 1957.
5. Buber, M. Guilt and guilt feelings. Psychiatry, **20**: 114–129, 1957.
6. Cannon, W. B. "Voodoo" death. Psychosom. Med., **19**: 182–190, 1957.
7. Fisher, S. and Cleveland, S. E. Relationship of body image to site of cancer. Psychosom. Med., **18**: 304–309, 1956.
8. Greene, W. A., Jr., Young, L. E. and Swisher, S. N. Psychological factors and reticuloendothelial disease. II. Observations on a group of women with lymphomas and leukemias. Psychosom. Med., **18**: 284–303, 1956.
9. Leshan, L. L. and Worthington, R. E. Personality as a factor in the pathogenesis of cancer. A review of the literature. Brit. J. M. Psychol., **29**: 49–56, 1956.
10. Richter, C. P. On the phenomenon of sudden death in animals and man. Psychosom. Med., **19**: 191–198, 1957.

NEUROPHYSIOLOGIC STUDIES OF PERSONALITY[1]

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In the field of personality, the identification and measurement of pertinent dimensions are one of the major problems. MacKinnon (10) has listed a number of dichotomous typologies, or bipolar factors, which have been proposed as fundamental dimensions of personality. Examples are the hysterical and obsessional types of Janet, the cycloid and schizoid types of Kretschmer, and the extraverted and introverted types of Jung. Although the typologies have been subject to a great deal of criticism, many of the terms engendered by them, such as "extravert," have found wide acceptance, suggesting a basis in everyday clinical observation. Over the past decade, the investigations of Eysenck and his group have indicated that some dichotomous typologies may represent the extremes of valid and measureable dimensions of personality. By applying factorial analysis to data obtained with a variety of test procedures, Eysenck isolated three personality factors, which he called: neuroticism, introversion-extraversion and psychoticism (3, 5). The investigations to be reported in this paper bear on a possible neurophysiologic basis for the introversion-extraversion dimension.

The present research arose from a previous study of the sedation threshold in psychoneurosis (16). The sedation threshold, which is an objective neurophysiologic determination of the amount of sodium Amytal required to produce certain EEG changes, was found to differentiate between various types of neurosis. Thresholds were low in patients with hysteria, intermediate in patients with mixed neurosis, and high in patients with anxiety states and neurotic depressions. These findings supported the hypothesis that the threshold was correlated with degree of manifest anxiety. However, they could also be taken to indicate a relationship between the threshold and the position of the patient on a personality continuum ranging from hysterical to obsessional. It was then noted that the order in which the sedation threshold arranged the psychoneuroses corresponded closely to the order in which Hildebrand (8) found them to be arranged by a battery of Eysenck's tests of introversion-extraversion. Furthermore, as Eysenck has recently pointed out (4), the sedation threshold results in psychoneurosis appeared to confirm, in every detail, predictions made from his theory that reactive inhibition is greater in hysterics than in dysthymics (obsessive-compulsives, neurotic depressions, anxiety states) (2).

From the parallels between Eysenck's results on introversion-extraversion and those obtained with the sedation threshold, it seemed reasonable to suggest that the sedation threshold might reflect the state of neural mechanisms involved in this dimension of personality. However, more direct studies of these relationships seemed desirable, as they had so far been inferred mainly from differences between diagnostic groups. Two investigative approaches were employed for this purpose in the present study. In the first, clinical ratings of hysterical-obsessional trend were compared with the sedation threshold. In the second, introversion-extraversion was measured by questionnaires and by determining the ease of formation of the conditioned eyeblink response; these measures were then compared with the sedation threshold. The question-

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naires used had contributed the greatest weight to Hildebrand's battery (8). The eyeblink conditioning measure was based on the work of Franks (6), who found that conditionability was correlated with questionnaire measures of introversion-extraversion, and differed in hysterics and dysthymics in the direction expected from Eysenck's reactive inhibition theory.

MATERIALS AND METHODS

Rating Study. Subjects were 308 patients, including all those classified as psychoneurotic in a consecutive series of 750; diagnoses and other details have been described elsewhere (14). There were 104 men and 204 women, aged from 16 to 71.

Questionnaire Study. Data-taking for this study had not been completed at time of writing. Results for the first 36 patients will be presented. The only factors influencing selection of these patients were availability for testing and absence of any clinical evidence to suggest the possibility of psychosis. There were 13 men and 23 women, ranging in age from 15 to 57, with a mean of 35 years. The group contained most types of psychoneurosis.

Sedation Threshold Procedure. The procedure has been described in detail in previous publications (13, 16). Sodium Amytal is injected intravenously at the rate of 0.5 mg. per kg. every 40 seconds until well after slurred speech is noted, while the frontal EEG is continuously recorded. The amplitude of the fast (15 to 30 c.p.s.) waves elicited by the drug is measured. Measurements in the earlier cases were done by a hand method (13); an electronic integrator (1) was used in about the last one-third of the "rating" series and in all of the "questionnaire" cases. The amplitude measurements are plotted against the amount of drug to yield a curve, which is usually of sigmoid shape and contains an inflexion point, preceding which the amplitude rises sharply and following which it tends to plateau. This point corresponds roughly to the onset of slurred speech. The sedation threshold is the amount of sodium Amytal, in mg. per kg. required to produce this inflexion point.

Ratings of Hysterical-Obsessional Trend. Ratings were based on case records, which usually consisted of assistant resident's admission note, intern's case history, and attending psychiatrist's discharge summary. As none of the histories was taken specifically for the purpose of assessing hysterical-obsessional trend, it was anticipated that some cases could not be rated. Two psychiatrists, who had not seen any of the patients, independently rated the case records without knowledge of the sedation threshold. The rating scale consisted of the following points: H3, H2, H1, M1, M2, O1, O2, O3. "H" referred to hysterical, "M" to mixed, and "O" to obsessional personality traits. Patients with clear hysterical conversion symptoms were to be rated H3 and patients with clear obsessive-compulsive symptoms were to be rated O3. The intermediate categories were intended to reflect varying degrees of intensity of one or other personality trend. Following are some illustrative descriptive phrases from the case records, which were used as a basis for rating: under *hysterical*, histrionic, manipulative, usually outgoing, immature, eager to communicate, exhibitionistic; under *obsessional*, meticulous, perfectionistic, conscientious, rigid, hard driving with guilt over failure, preoccupied with detail, afraid of losing control.

Introversion-Extraversion Scales. The Rhathymia (R) and Social-Introversion (S) Scales of the Guilford inventory of factors S, T, D, C and R (7) were used to measure introversion-extraversion. Individual questions were typed on cards; the subject answered them as yes, no or uncertain, by sorting them into three appropriately labeled compartments of a box. The cards were presented in a random order. A French translation was used for French-speaking patients; the French version seemed to give approximately the same results as the English one when both were given to a few

bilingual persons. For convenience in presenting the statistics, the raw scores for each of the scales were converted into standard C scores, according to tables supplied in the test manual. The C score statistics did not differ to any extent from those based on the individual raw scores, which were also worked out. As the C scores in the manual were arranged in such a way that they increased with increasing extraversion, they were reversed in order to avoid negative correlations. Also the C scores for R and S were added to provide a combined C score with a possible range from 0 to 20; the higher the combined C score, the greater the degree of introversion.

Conditioning Procedure. In the main, Frank's procedure was followed (6). The conditioned stimulus was a tone of 1100 cycles, produced by an Ediswan oscillator, Type R666, at an output of 22.5 volts, and delivered through S. C. Brown Type K moving coil headphones. The unconditioned stimulus was an air puff to the cornea. The air source was a compressed air supply, with the valve at the main outlet set so that the pressure was 2 ± 0.5 lb. Overall timing was controlled by a R. W. Cramer switch, Type M8 120S with a 0.5 r.p.m. motor, which was set so that 8 interstimulus intervals varying from 11 to 19 seconds would be repeated serially. The tone lasted 650 milliseconds, and, in reinforced trials, it was followed immediately by an air puff, lasting 275 milliseconds. Release of the air was effected by means of an Asco air valve, with relay activated by an electronic timing circuit. The air tube was held in place by a plastic frame attached to the headphones. There were 48 stimuli in the conditioning series; 30 included both tone and air puff and 18 consisted of tone alone. Before the first stimulus of the conditioning series, there was a preliminary series of stimuli; the first 3 were tone alone, then there were 3 air puffs alone, and finally 3 tones alone. Following the conditioning series, there was an extinction series consisting of 10 unreinforced tones.

The retinocorneal potential from two electrodes near the eye provided a recording of eyeblink on one channel of a Grass EEG. The subject was seated during the conditioning procedure; some degree of eye fixation was obtained by having the subject look at a coat hook on the wall in front of him. The experimenter could observe the subject through a window. The subject's room was semidark. In evaluating the conditioning records, all eyeblink deflections of at least 3 mm. amplitude, beginning from 500 to 1000 μseconds after the onset of the tone, were scored as a response. Subjects with 3 or more out of a possible 6 responses to the tones preceding the conditioning series were rejected.

RESULTS

Hysterical-Obsessional Rating. One or the other psychiatrist was unable to rate 84 of the 308 cases. To obtain some estimate of the degree of agreement between raters in the remaining 224 cases, the H3 to O3 scale was treated as an eight point rating scale and the product-moment correlation between the two ratings was determined. The correlation coefficient was 0.78, indicating reasonably good agreement.

Again with the ratings determined as an eight point scale, the correlation between the mean of the two ratings and the sedation threshold was determined. The correlation coefficient was 0.53, which is highly significant statistically and indicates that the sedation threshold was positively correlated with hysterical-obsessional trend. Figure 1 shows the mean hysterical-obsessional rating for each sedation threshold. The graph shows that thresholds of 3.0 or less were obtained in patients generally rated as hysterical, and thresholds of 4.5 or more were obtained in patients generally rated obsessional. Figure 1 also suggests that the sedation threshold discriminates only three, or

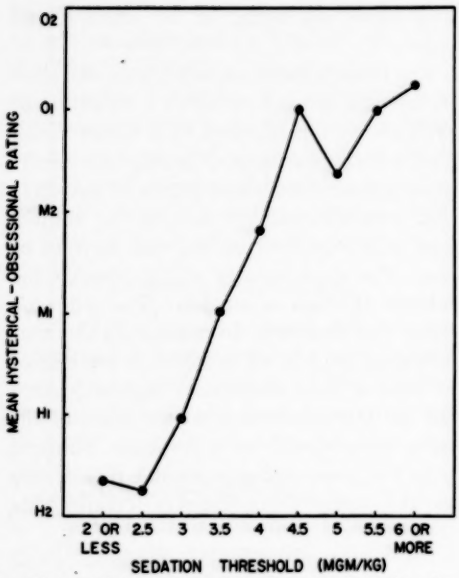

FIG. 1. Mean hysterical-obsessional rating by sedation threshold, 224 patients. Rating for each patient was the mean of two psychiatrists' ratings.

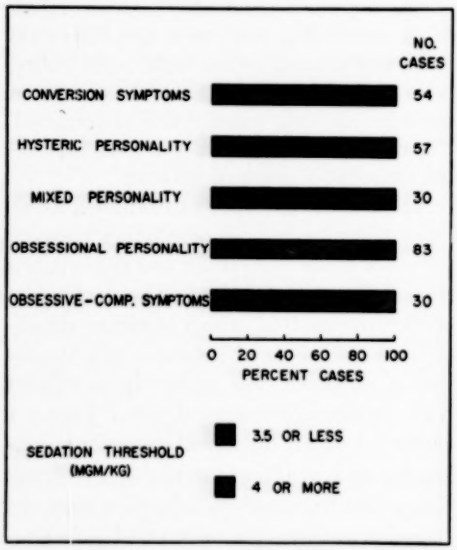

FIG. 2. Relationship between sedation threshold and main reason for hysterical-obsessional ratings made by one psychiatrist. Note that differences between ratings made because of symptoms are greater than differences between ratings based on personality characteristics.

at the most four, points on a hysterical-obsessional continuum.

It was of some interest to determine whether the correlation between hysterical-obsessional trend and the sedation threshold was based more upon symptoms or upon assessments of behavior characteristics. One of the raters was asked to indicate the basis for his ratings in these terms. The reasons could be classified into five categories: conversion symptoms, obsessive-compulsive symptoms, and either hysterical, mixed, or obsessional personality characteristics. Figure 2 shows the proportion of above and below average sedation thresholds for each of these categories in the 254 patients assigned ratings by this psychiatrist. Sedation threshold differences were greatest between patients with frank conversion and obsessive-compulsive symptoms. The differences were less marked between the groups classified on personality characteristics alone, but the trend was statistically significant at better than the 1 per cent level of confidence. Thus, although it appeared that symptoms provided a firmer basis for discrimination with respect to the sedation threshold, there was also a definite relationship between the threshold and personality evaluations based on behavioral characteristics.

As the ratings were based on heterogeneous case materials gathered in a nonstandard fashion, it seemed reasonable to assume that those subjects to whom both psychiatrists assigned the same ratings might offer some approximation of the true relationship between the sedation threshold and hysterical-obsessional trend. Figure 3 shows the distributions of sedation thresholds for all those cases assigned either an H or O rating by both psychiatrists. There was relatively little overlapping between these groups with concordant ratings. The biserial correlation coefficient for the data in Figure 3 was 0.84; this coefficient is spuriously high because the mixed group was omitted, but it gives some indication of the possible relationship.

Guilford Introversion Score. The 36 patients for whom questionnaire scores and sedation thresholds were available contained a somewhat greater than usual number of patients with high thresholds, thus restricting the possible range of variation. Even with a restricted range, the coefficient for the correlation between the threshold and the introversion C score, which was 0.60, was highly significant statistically. The S scale contributed more to the correlation than the R scale. Figure 4 illustrates the relationship between the sedation threshold and the introversion score. These data confirm the hypothesis that the sedation threshold is positively correlated with degree of introversion.

Conditioning. Acceptable conditioning results were available for only 22 of the 36 patients. It was necessary to reject 7 patients because of apparatus breakdown during the conditioning experiments, and 7 more because they gave three or more blink responses during the six preconditioning presentations of the tone alone. Taking the total number of conditioned responses during the unreinforced trials of the conditioning and extinction series as a total conditioning score, the correlations between this score and the introversion C score and sedation threshold were determined. The coefficient for conditioning score *versus* introversion was 0.45, and for conditioning *versus* sedation threshold was 0.23. The former was significant at the 5 per cent level of confidence, while the latter was not significant.

The absence of a significant correlation between conditioning and sedation threshold suggests that these two procedures measure factors which are not similar. If one takes conditioning as another measure of central nervous system function, it is a matter of interest to determine how well introversion-extraversion could be predicted by a combination of the sedation threshold and the conditioning tests. In the 22 subjects for whom all three sets of data were available, the coefficient of multiple correlation between the introversion score and a combination of the sedation threshold and the conditioning score was 0.67. This was significant at the 1 per cent level of confidence.

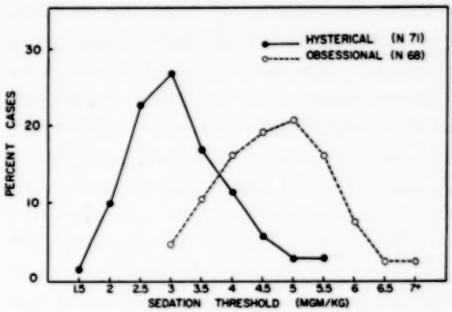

FIG. 3. Percentage distributions of sedation thresholds in patients classed as hysterical or obsessional by both raters.

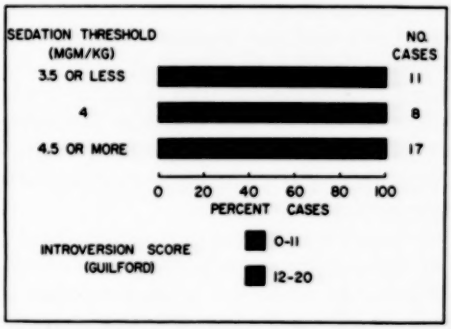

FIG. 4. Relationship between sedation threshold and introversion (Guilford combined C score for R and S scales).

DISCUSSION

Present data support the conclusion that the sedation threshold is correlated with degree of hysterical-obsessional trend or introversion-extraversion. The results are in agreement with Jung's (9) view that the characteristic neurosis of the extrovert is hysteria, whereas that of the introvert is psychasthenia, and they confirm Hildebrand's (8) results showing that hysterics and dysthymics differ on measures of introversion-extraversion. Franks' (6) findings with respect to conditionability and introversion-extraversion are also confirmed, al-

though the hypothesis that the sedation threshold would be correlated with conditionability was not supported by the data.

It is possible that our failure to demonstrate a relationship between conditionability and the sedation threshold may be due to undiscovered technical faults in the conditioning procedure, or that a larger series will yield more positive results. However, these possibilities seem dubious in view of the fact that the present correlation of 0.45 between the conditioning and introversion scores was almost identical with the correlation which Franks found. The present negative conditioning data are not critical for the theory that the dimension of introversion-extraversion is associated with a dimension of central nervous excitation-inhibition, insofar as the sedation threshold, which is a more direct measure of central excitability, was definitely correlated with introversion-extraversion.

In previous studies of the sedation threshold in nonpsychotic subjects, it seemed appropriate to stress the positive correlation between the threshold and degree of manifest anxiety (16, 17). The relationship between the threshold and hysterical-obsessional trend, which present results confirmed, was also noted. As it would be desirable to avoid the problems raised by multiple concepts, one might attempt to bring these two correlates of the sedation threshold together, if it could be demonstrated that manifest anxiety is really dependent upon introversive tendencies. This is a possibility which agrees with much clinical experience, but one cannot ignore the fact that hysterics manifesting apparent anxiety reactions are by no means uncommon. Another reason for retaining the anxiety correlate comes from data showing that, when patients with anxiety states and high sedation thresholds responded to therapy with reduction of anxiety, the sedation threshold decreased (15). To account for these facts, it was suggested that there are several neurophysiologic mechanisms of anxiety, that the "choice" of mechanism is linked with personality structure, and that the sedation threshold reflects the activity of that anxiety mechanism predominating in obsessional or introverted persons (15). However, if retest studies were to show that a decrease in sedation threshold is accompanied by a corresponding decrease in both anxiety and introversion, it would be possible to regard the personality factor as the primary correlate of the threshold. It should be possible to carry out the research necessary to clarify this issue.

Eysenck (4) has drawn attention to a pharmacologic implication of the sedation threshold; it suggests that the position of a person on the introversion-extraversion continuum may be perhaps the most important factor influencing his therapeutic dosage requirements for a stimulant or depressant drug. Impressions gained by one of us from clinical experience with sedatives seem to substantiate this view. In hysterical patients, small doses of sedatives are often adequate, whereas the larger doses, which are required by dysthymics, tend to produce disturbing side effects. These side effects are often reported in the form of exaggerated complaints, which may sometimes be interpreted by the physician as a need for more sedation; if more is given, this may lead to further side effects, and so on. This differential effect of sedatives in hysterics and dysthymics is allied to Pavlov's observations on the quantitative therapeutic requirements of bromides in dogs with experimental neuroses (11, p. 92). A practical clinical application would be to use personality assessment as a guide to sedative dosage.

Although the exact neurophysiologic function reflected by the sedation threshold is not certain, it most probably measures a time characteristic of neuronal excitability (12). In demonstrating that introversion-extraversion is correlated with a neurophysiologic factor of this order, the present study provides strong support for a theoretical ap-

proach to personality which is orientated along neurophysiologic lines.

SUMMARY

The purpose of this study was to test the hypothesis that the sedation threshold is correlated with a personality factor, similar to Eysenck's introversion-extraversion dimension or, in neurotics, a hysterical-obsessional continuum. In one part of the study, two psychiatrists independently rated 308 case records for hysterical-obsessional tendency. Their ratings were significantly correlated with the sedation threshold, a high threshold being associated with obsessional tendencies and a low one with hysterical tendencies. Another investigative method used was to correlate the sedation threshold with questionnaire scores of introversion-extraversion (Guilford R and S scales) in 36 neurotic patients and with ease of conditioned eyeblink formation. The threshold was significantly correlated with the questionnaire scores in the predicted direction, high thresholds being associated with introversion. The threshold was not significantly correlated with conditionability, although high introversion on the questionnaire was associated with greater conditionability. The main conclusion reached from the findings was that there is an objectively demonstrable neurophysiologic basis for the introversion-extraversion dimension.

Acknowledgments. Thanks are due to Dr. J. F. Davis for designing the aparatus used in this study, to Dr. A. L. Jones for rating the case records, to Dr. J. L. Lapointe for translating the Guilford scales into French, and to Herbert Lorenz and Genevieve Servin for technical assistance.

REFERENCES

1. Davis, J. F. Low frequency analyzers in electroencephalography. Paper (No. 56-24-1) presented at the Instrument Society of America Meeting, September, 1956.
2. Eysenck, H. J. A dynamic theory of anxiety and hysteria. J. Ment. Sc., **101**: 28, 1955.
3. Eysenck, H. J. *Dimensions of Personality*. Routledge & Kegan Paul, Ltd., London, 1947.
4. Eysenck, H. J. Drugs and personality. I. Theory and methodology. J. Ment. Sc., **103**: 119, 1957.
5. Eysenck, H J. *The Scientific Study of Personality*. Routledge & Kegan Paul, Ltd., London, 1952.
6. Franks, C. M. Conditioning and personality. A study of normal and neurotic subjects. J. Abnorm. & Social Psychol., **52**: 143, 1956.
7. Guilford, J. P. An inventory of factors S, T, D, C, R. *Manual of Directions and Norms*, Sheridan Supply Co., California, 1940.
8. Hildebrand, H. P. A factorial study of introversion-extraversion by means of objective tests. Ph.D. Thesis, University of London Library, 1953.
9. Jung, C. G. *Psychological Types*. Routledge & Kegan Paul, Ltd., London, 1924.
10. MacKinnon, D. W. Personality and the behavior disorders. In *The Structure of Personality* (J. McV. Hunt, editor). Ronald Press Co., New York, 1944, Ch. 1.
11. Pavlov, I. P. *Conditioned Reflexes and Psychiatry* (Transl. by W. H. Gantt). International Publishers, New York, 1941.
12. Shagass, C. A measurable neurophysiological factor of psychiatric significance. Electroencephalog. & Clin. Neurophysiol., **9**: 101, 1957.
13. Shagass, C. The sedation threshold. A method for estimating tension in psychiatric patients. Electroencephalog. & Clin. Neurophysiol., **6**: 211, 1954.
14. Shagass, C. and Jones, A. L. A Neurophysiological Test for Psychiatric Diagnosis. Results in 750 patients. Amer. J. Psychiat. (in press).
15. Shagass, C., Mihalik, J. and Jones, A. L. Clinical psychiatric studies using the sedation threshold. J. Psychosom. Res., **2**: 45, 1957.
16. Shagass, C. and Naiman, J. The sedation threshold as an objective index of manifest anxiety in psychoneurosis. J. Psychosom. Res., **1**: 49, 1956.
17. Shagass, C. and Naiman, J. The sedation threshold, manifest anxiety and some aspects of ego function. A. M. A. Arch. Neurol. & Psychiat., **74**: 379, 1955.

THE CINGULATES AND BEHAVIOR[1]

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This study is one of a series on the behavioral effects of ablation of specific neo-, paleo- and subcortical areas of the brain.

METHODS

Controls. The spontaneous behavior and learning capacities of 9 cats and 11 monkeys were observed for from 3 to 12 months. During this time the animals were put through a series of increasingly complicated tests involving discriminative response to visual, auditory and temporal cues, the pressing of levers to earn food rewards, and in the case of the monkeys, problems involving immediate memory and the perception of visual configurations. The data were rated on 30 highly reliable six point scales of specific patterns of behavior (7).

Induction of Neuroses. Four of the cats were subjected to adaptational conflicts induced by condenser shocks given through the floor of a special apparatus (6) 1 to 15 times at the moment of food taking. Four of the monkeys were similarly subjected from 1 to 30 times to the shock experiences and/or the sudden exposure to a toy rubber snake in the food box. As described elsewhere (6) these conflictual experiences produced acutely disruptive reactions followed by persistent neurotic aberrations such as apprehensiveness, phobias, altered feeding patterns, severe organic dysfunctions, and disturbed social interactions.

Operative Procedures. Lesions were placed by suction bilaterally in a sterile open field operation with the animals under sodium pentobarbital anesthesia.[3] Area 23 was largely destroyed, with minimal damage to adjacent areas in 3 normal cats and 3 cynamologos monkeys and in 2 neurotic cats and 2 rhesus monkeys. Area 24 was similarly ablated in 2 normal cats and 4 normal rhesus monkeys and in 2 neurotic animals of both species.

Postoperative Procedures. Four to 12 days after operation routine observations and testing were resumed and continued for from 9 months to over 2 years, during which period the animals were also subjected to neurotogenic stimuli. Except for the three cynamologos monkeys still being studied, the brains of all the animals have been sectioned and stained for histologic reconstruction of the lesions.

RESULTS

Ablations in areas 23 or 24 in the cat or the monkey produced in the main qualitatively similar effects which may be summated, except where specific differences exist, as follows.

Amnesia. In contrast to lesions in the amygdalas in the monkey, the mediodorsal thalamic nuclei in the cat and the orbitofrontal area in both species, ablations of either the anterior or posterior cingulate gyri produced very little or no impairment of preoperative learning as tested by our methods.

Performance on Learned Problems. However, the performance of the area 23 cats during their daily 20 trials on previously mastered problems became inconsistent and

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[3] These operations were performed by Drs. Paul J. Hutt and Arthur Kling.

erratic; cats with lesions in area 24 showed similar but lesser impairments. The monkeys made only a few more errors after cingulotomy, although many of their responses appeared precipitate and poorly timed.

New Learning. The cingulotomized cats and monkeys mastered new problems with approximately the same speed but with less precision and efficiency than did normal controls.

Motor Activity. After cingulotomy normal patterns of feeding, play, and approach or avoidance of mates and human beings, became hurried or diffuse. Area 24 monkeys in particular were impatient about their turn in the experimental apparatus, frequently would not wait for the proper cues before attempting to work for their food rewards and showed other evidences of impaired timing and efficiency.

Motivation. Concurrently, area 23 cats seemed less motivated to work for food rewards on simple as well as more complicated problems than they had been preoperatively or as compared with a control group. The area 23 cingulotomized animals took longer for the daily 20 trials and significantly oftener (beyond the 0.001 level of confidence) would not finish a day's run or would not work at all. The motivation of the area 24 cats seemed diminished on simple tasks and was low on more complex ones. The area 23 rhesus monkeys also showed a moderate decrease on simple tasks and more on complex ones; however, the three cynamologos monkeys and the area 24 monkeys showed no change in motivation following ablation.

Social Adaptations. The male cats with lesions in areas 23 or 24 showed considerable inter-cat aggression; area 23 cats were also more irritable toward human beings, although the area 24's were only slightly so. Similarly, area 23 and area 24 monkeys showed respectively increasing interanimal irascibility, particularly in animals which had never adapted well to the laboratory.

Aversive Responses. The cats with lesions in either cingulate area showed slightly lowered thresholds for startle and fear responses. All the area 24 monkeys and the two rhesus monkeys with lesions in area 23 likewise showed marked susceptibility to these responses. The thresholds of the three cynamologos monkeys were substantially raised; however, they were still low in comparison with other monkeys since these animals had made a poor preoperative adaptation to the laboratory and had shown ready startle and fear.

Effects of Relative Isolation. During two periods of 3 or 4 weeks each the animals were kept continually confined to their home cages. For the cats this meant not only a lack of practice on learned tasks but a minimum of human contact and no direct access to other animals. The monkeys were similarly deprived of the daily routine of being brought to the laboratory but still had much of their usual contact with colony mates and man. On being retested after these intervals of isolation, all of the cats showed decreased consistency of performance on learned problems from day to day, and in the area 23 cats some of this variability persisted. The area 23 monkeys showed a slight and the area 24 animals a moderate increase in daily errors. All the animals showed diminished motivation toward working for food rewards for the ensuing 3 to 10 weeks, and in the area 23 cats this effect was permanent. The cingulotomized cats after isolation were less friendly toward other cats and man and remained to some degree antagonistic. The area 23 monkeys were also slightly and the area 24 moderately more irritable after returning to the laboratory, but these effects disappeared with time.

Maternal Behavior. One of the area 24 monkeys gave birth to a male baby which she was allowed to keep and nurse for 7 months. During the latter weeks of this period the baby made efforts to get its portion of plentifully available solid food,

particularly fruits, but the mother, instead of sharing such edibles with her offspring, seized almost all he had managed to obtain, even from his mouth. Nevertheless, she did not abuse the baby physically as had been the case with two amygdalectomized mothers, and whenever even familiar human beings came near, she would scream and grab up the infant. Yet she was not antagonistic toward the experimenter after it was taken from her, nor did she show other signs of missing it as a majority of rhesus mothers do. The infant was retarded at least 50 per cent in physical and motor development.

Effects on Neurotic Patterns. Neurotic cats showed only slight reduction in apprehensiveness and phobic responses after lesions in either cingulate area, though the animals became a little more friendly toward other cats and human beings. The neurotic monkeys, in contrast to all our adult controls with lesions elsewhere in the brain, showed no significant postoperative changes in their neurotic patterns, with the exception that the three cynamologos monkeys were considerably relieved of their generally disturbed behavior. On the other hand, as in the case of lesions elsewhere (7, 8, 10), all the animals were somewhat more amenable to retraining and other modes of influencing their neurotic aberrations.

Resistance to the Postoperative Induction of Neuroses. The resistance to the induction of neurosis measured by the number of traumas and the number of days necessary to produce ratings indicative of chronic neurosis was moderately lower for both groups of cats. It was slightly lower for the area 23 rhesus monkeys and three of the area 24's, and markedly so for the cynamologos monkeys; however, no controls were available for this species and we would expect them to show less resistance on the basis of their poor adaptation to the laboratory and their somewhat inferior learning scores (8). However, one of the area 24's showed resistance far above the average for the normal group, and in one other case, unique in our quarter of a century of experimentation, we were not able to produce more than transient manifestations of fear and moderate but persistent hyperalertness in a cingulotomized monkey after 6 months of effort.

DISCUSSION

Ward (15, 16) and Glees, Cole, and Whitty (2) reported that monkeys with lesions in area 24 grew relatively tame, lost their fear of man and disregarded cage mates to the point of sitting or walking on them. Ward thought his operated monkeys were more "inquisitive" while Glees *et al.* characterized their animals as more "restless and hyperactive." Smith (12) also described increased "tameness" in his group of cingulectomized rhesus monkeys. Kennard (3), working with cats, reports as a result of cingulectomy a syndrome characterized by "confused, perseverative, obsessive behavior, and a plastic tendency whereby the animal may be posed for long periods of time in bizarre position," lowered thresholds for rage reactions, and some elements of postural confusion. Barris (1), also working with cats, reported a similar picture. As we have pointed out elsewhere (7), such variable effects are attributable not only to variations in the site and extension of the lesions, altered blood supply and other anatomic factors, but also to both the individual characteristics and the pre- and postoperative experiences of each animal.

Ward suggested that anterior cingulate ablation in man is equivalent to lobotomy since the operation separates the anterior cingulates from the anterior thalamic nuclei much as the frontal areas are separated from the mediodorsal thalamic nuclei in lobotomy. Clinically Le Beau (4) and his group reported that in more than 50 patients cingulectomy favorably affected "obsessive-compulsive" symptoms as well as

"intractable irritability, aggressiveness... violence and agitation, especially when associated with chronic epilepsy;" without the "classical [postlobotomy] euphoric and careless behavior," mental confusion or restlessness. Tow and Whitty (14) and Tow and Armstrong (13) found that cingulectomy reduced perseveration in both affective and cognitive spheres and produced a general disinhibition (14) and "relief of tension" or loss of subjective apprehensiveness persisting from 3 up to 18 months (13). Livingston (5) reported that a majority of his 55 patients showed a diminution of hostility and fear and striking alterations of mood toward pleasantness, contentment, normal affective tone and reactivity; these effects abated, but there was a tendency to reimprovement. Siris (11) also felt that the results of interrupting thalamocingulate projections were favorable. It is evident, then, that although these observers recommend cingulectomy in various conditions, each reports a somewhat different constellation of behavioral effects of varying duration, indicating that even a preliminary assessment of the role of the cingulates cannot as yet be made.

SUMMARY

Nine cats and 11 monkeys were studied for from 3 to 12 months preoperatively for (*a*) spontaneous behavior (*b*) learning capacity and (*c*) the neurotogenic effects of motivational conflicts. Ablation of cingulate areas 23 and 24 then produced the following results:

1. Minimal amnesia for previous learning, but increased incidence of error and impaired precision of acquiring new skills.

2. A tendency to diffuse and precipitate activity.

3. Diminished motivation, especially for initiating or completing goal directed tasks, with the exception of area 24 monkeys.

4. Moderately increased aggressivity toward other animals and man.

5. Lowered thresholds of startle and fear, except in three cynamologos monkeys.

6. An accentuation of the effects of isolation in exacerbating the above reactions.

7. In one instance, maternal preemption of food at the expense of a nursing baby.

8. Minimal or no relief of phobic, regressive, socially maladaptive, and other aberrant behavior in the neurotic animals, but with greater amenability to retraining and other therapy.

9. Generally increased susceptibility to the reinduction of experimental neuroses, again with the exception that two area 24 monkeys showed an increased tolerance to conflictual experiences and in one of these we were unable to induce a neurosis even after 6 months of effort.

The theoretical and clinical significance of these findings is briefly discussed.

REFERENCES

1. Barris, R. W. Cataleptic symptoms following bilateral cortical lesions in cats. Am. J. Physiol., **119**: 213–220, 1937.
2. Glees, P., Cole, J., Whitty, C. W. M. and Cairns, H. The effects of lesions in the cingular gyrus and adjacent areas in monkeys. J. Neurol. Neurosurg. & Psychiat., **13**: 178–190, 1950.
3. Kennard, Margaret A. Effect of bilateral ablation of cingulate area on behaviour of cats. J. Neurophysiol., **18**: 159–169, 1955.
4. Le Beau, J. Anterior cingulectomy in man. J. Neurosurg., **2**: 268–276, 1954.
5. Livingston, K. E. Cingulate cortex isolation for the treatment of psychoses and psychoneuroses. Res. Publ. A. Nerv. & Ment. Dis., **31**: 374–378, 1953.
6. Masserman, J. H. and Pechtel, C. Neuroses in monkeys. Ann. N. Y. Acad. Sc., **56**: 253–265, 1953.
7. Masserman, J. H. and Pechtel, C. How brain lesions affect normal and neurotic behavior. Am. J. Psychiat., **112**: 865–872, 1956.
8. Masserman, J. H. and Pechtel, C. Neurophysiologic and pharmacologic influences on experimental neuroses. Am. J. Psychiat., **113**: 510–514, 1956.
9. Masserman, J. H., Levitt, M., McAvoy, T., Kling, A. and Pechtel, C. The amygdalae and behavior. Read at 113th Annual Meeting of the Am. Psychiat. A., May 16, 1957, Chicago, Ill.

10. Pechtel, C., Masserman, J. H., Schreiner, L. H. and Levitt, M. Differential effects of lesions of the mediodorsal nuclei of the thalamus on normal and neurotic behavior in the cat. J. Nerv. & Ment. Dis., **121**: 26–33, 1955.
11. Siris, J. H. Thalamocingulate fasciculotomy. Psychiat. Quart., **25**: 251–256, 1951.
12. Smith, W. K. The results of ablation of the cingular region of the cerebral cortex. Fed. Proc., **3**: 42, 1944.
13. Tow, P. M. and Armstrong, R. W. Anterior cingulectomy in schizophrenia and other psychotic disorders. Clinical Results. J. Ment. Sc., **100**: 46–61, 1954.
14. Tow, P. M. and Whitty, C. W. M. Personality changes after operations of the cingulate gyrus in man. J. Neurol. Neurosurg. & Psychiat., **16**: 186, 1953.
15. Ward, A. A. The cingular gyrus. Area 24. J. Neurophysiol., **2**: 13–23, 1948.
16. Ward, A. A. The anterior cingulate gyrus and personality. In: The frontal lobes. Res. Publ. A. Nerv. & Ment. Dis., **27**: 438–445, 1948.

PATTERN, STABILITY AND CORRELATES OF PHOTIC-ELECTROENCEPHALOGRAPHIC ACTIVATION[1]

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The increasing use of photic stimulation by psychiatric investigators during the past decade has emphasized the need for greater knowledge regarding the nature and variation of the individual electroencephalographic (EEG) patterns of driving and activation and their stability over time. Earlier investigations were without benefit of an analyser and left open the question of whether photic driving was indeed a universal phenomenon until Kooi (10) reported in 1957 that all 90 of his control subjects showed some driving. The significance and stability of photic driving over time however warrents further exploration.

Few studies have attempted to relate photic driving to resting EEG and clinical variables and these few studies have not shown consistent results. Some authors (13, 15) have stated that the driving pattern is related to the predominant activity of the resting EEG. Early studies from our laboratory (21) and by Shagass (18) suggested a relationship between driving and/or harmonics at fast frequencies and the presence of anxiety. Findings of Mundy-Castle (13) suggest that a greater following in the beta range and in the 2nd and 3rd harmonics is related to the temperament variable called primary functioning. Shagass (18) followed patients during psychotherapy and found shifts in the driving pattern that appeared related to the day-to-day changes in mood. Such fluctuations had been earlier suspected by Walter (25), and Mundy-Castle (14) reported results from a psychotic patient in whom an abnormal pattern induced by photic stimulation later disappeared after a course of insulin given together with psychotherapy. These latter studies would have had greater significance had more data been available on the stability and reliability of driving and activation patterns.

Studies of EEG "activation" by photic stimulation have been of more clinical interest than photic driving. Here attention has been focused upon the appearance of slow, spiking or paroxysmal disorder in the EEG evoked by exposure to the flashing light. Usually the elicitation of such patterns is facilitated by repeated injections of a convulsant drug (Metrazol, Fazole, etc.). The smaller the amount of drug needed (*i.e.*, the lower the "activation threshold") the more likely is there a diagnosis of paroxysmal disorder (4). The occurrence of such patterns, produced by light alone, without any drug would seem to imply the lowest possible threshold (4). Low thresholds have been reported to relate significantly not only to seizure disorder (4, 6, 11) but also to schizophrenia (2, 4, 8, 12) to hysteria (4) and to behavior disorders in children (14). However, we have observed that several healthy young males with no personal or family history of convulsive disorder have

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had their first and only seizure induced by light alone (21). We also failed to corroborate reports of a lowered convulsive threshold in schizophrenia (19). Both these findings have raised serious questions as to the significance of this type of activation.

The present studies were conducted in order to increase our understanding of such phenomena as well as to establish for future studies, baseline data on the pattern and stability of photic driving of the EEG and of light induced activation. Some observations on possible psychologic and physiologic correlates are also presented, together with driving and activation data from a carefully selected psychiatric population.

PROCEDURE

SUBJECTS

The subjects for the present study were the total freshman class of a local graduate school (N = 182, mean age 20.2, standard deviation 1.02). From this total group 50 were selected for repeat examinations over a three-year period. The follow-up sample was selected with reference to degree of activation by photic stimulation and basic EEG pattern. This was done by visual inspection of the records without the aid of a quantitative scale. The representativeness of the initial selection is indicated in Table 1. The cases are distributed on a five-point scale developed subsequently to measure degree of activation and are also listed according to clinical EEG classification of resting record, prior to photic stimulation, read by an experienced electroencephalographer.

TABLE 1

Activation Response and EEG Classification

	Follow-Up Group N = 50		Residual Group N = 132	
Activation Response				
	N	*Per cent*	*N*	*Per cent*
Normal	38	76	103	78
Questionable paroxysmal	8	16	15	11.4
Paroxysmal	2	04	10	07.6
Definitely paroxysmal	2	04	4	03
EEG Classification				
Normal	38	76	110	83
S_1	4	08	7	05
S_2	2	04	0	00
F_1	1	02	1	01
F_2	0	00	0	00
Paroxysmal	1	02	4	03
Mixed fast slow	0	00	9	07
Low voltage fast	4	08	1	01

PHOTIC STIMULATION AND EEG EXAMINATION

Photic stimulation was produced by a disk episcotister developed in our laboratory. The light source was a Westinghouse projector lamp, 1000 watts, 120 volts (T-12 bulb, C-13-D filament) mounted in a 16-mm. movie projector housing with internal polished focusing reflector. The light beam was focused by a suitable condenser system to give a 30-inch circle of light on a thirty-six inch, flashed opal-glass screen located 4½ feet from the light source. The one-inch aperture in front of the light housing was intermittently interrupted by a rotating aluminum wheel. The light dark ratio was 1:1. The frequency of stimulation could be varied at will from 3 to 33 flashes per second (f.p.s.). The intensity of light measured on the distal side of the opal glass screen was 200 foot candles centrally and fell roughly to 100 foot candles peripherally. All subjects were seated as close to the screen as possible, usually at a distance of 6 to 12 inches. The whole visual field was thus filled with the light stimulus.

A Gilson 8-channel electroencephalograph was used with conventional calibration and filtering. Scalp-to-scalp recording by means of needle electrodes was employed. The parieto-occipital electrode pair (which is the most critical for studies of response to photic stimulation) was carefully placed in an attempt to keep the location of the leads comparable from person to person and from trial to trial. The occipital lead was placed 1 cm. above and 1 cm. lateral to the inion.

The parietal lead was placed above the external auditory meatus and lateral from the sagittal plane one third of the distance from the mid-vertex to the external auditory meatus.

The EEG recording procedure was as follows:

1. Ten minutes of resting record taken with eyes closed.
2. Five minutes of resting record taken with eyes open.
3. Photic driving survey (with eyes open) consisting of a 40-second exposure, with a 40-second interval between each exposure, to each of the 24 different frequencies (3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 13.5, 15, 16.5, 18, 20, 22, 24.5, 27, 30, 33).
4. EEG recordings during hyperventilation. (This section is not analyzed in this report.)

The brain wave activity recorded from the right parieto-occipital leads was electronically analyzed, and representative strips from this record were selected in a predetermined fashion for measurement. The analyzer used has been described elsewhere (23). This analyzer yields a profile of the amount of activity at each of 24 frequencies within a 10-second interval. The pen deflection at each frequency is proportional to the average microvoltage at that frequency multiplied by the percent time occurrence of that frequency in the 10-second interval.

The following strips were selected for measurement: (1) six consecutive 10-second strips of eye-closed resting (*i.e.*, the last minute of artifact free recording; (2) four consecutive strips from the recording taken with eyes open (this was used as a baseline against which the effect of photic stimulation was evaluated); (3) four consecutive strips for each of the frequencies in the driving survey.

These analyzer data were used in computing the basic driving profiles, the relationship of spontaneous activity to photic driving and in the study of stability of response to photic stimulation. Photic driving is defined in this paper as the amount of cortical activity present during photic stimulation minus the spontaneous activity recorded during a resting period (*i.e.*, the increment of activation produced during the period of stimulation). Thus three EEG measures will be referred to in this paper, resting EEG, photically stimulated EEG, and driving, which is the difference between the resting and photically stimulated EEG. The subjects' eyes were open both at rest and during stimulation.

RESULTS

A. PATTERNS AND STABILITY OF PHOTIC DRIVING

As these data have been presented in detail elsewhere (9) only a summary will be presented here. Photic driving was found to be a common response seen in all subjects at some frequencies. The median curves for basic driving (driving at flicker frequency) and second, third and fourth harmonic driving curves are presented in Figure 1. The basic driving profile indicates that 50 per cent of the group exhibit a definite one to one driving response (8 mm. or greater) at all frequencies between 5 to 30 c.p.s. The curve for the first quartile, not shown in Figure 1 but presented earlier (9) indicate that 75 per cent show a driving response between the frequencies 8.5 and 24 c.p.s. which suggests that between these frequencies is the best range for study of photic driving. The peak response occurs in the region from 8 to 10 c.p.s. Relatively few individuals have one to one driving at the very low frequencies (below 4 c.p.s.). The value taken here to indicate a significant driving response (*i.e.*, 8 mm. pen deflection) is, of course, arbitrary but it is doubtful whether anything less than this could be detected in the unanalyzed EEG.

Not only do the low frequencies not respond, in general, to direct stimulation but activity at these low frequencies appears actually to be somewhat suppressed in many cases by flicker at a higher frequency. Thus

the sub-harmonics of frequencies up to about 15 c.p.s. are in general negative for more than 50 per cent of the sample, indicating that there was more activity in the basic eyes-open EEG recording in the frequencies 3 to 7.5 c.p.s. than occurred when these frequencies were sub-harmonics of the flicker frequencies.

Third and fourth harmonic responses (Figure 1) do occur in some people at most frequencies. However, it is interesting that flickering at 3 and 3.5 c.p.s. produces practically no response at 9 and 10.5 c.p.s., the frequencies most likely to respond to one-to-one driving. It may be noted from Figure 1 that, in general, there is no tendency for any one frequency or group of frequencies to exhibit both peak one to one and harmonic responses. The peak response for one to one driving is around 10 c.p.s., that for second harmonics is about 13 c.p.s., and for third harmonics is around 24 c.p.s. To be consistent with the resonant theory of driving, the peak harmonic responses should have been at 20 c.p.s. and 30 c.p.s. An examination of individual records also reveals no trend toward consistently greater responsivity at certain frequencies. However, there is a tendency for those who show the greatest one to one driving at high frequencies to also have the most average fourth harmonic response. Thus average driving in the region 15 to 22 c.p.s. is correlated 0.28 with fourth harmonic driving at lower frequencies of stimulation and average driving from 24.5 to 33 c.p.s. is correlated 0.37 with the appearance of fourth harmonics.

While Figure 1 gives some idea of the pattern of median driving response at each frequency, it does not reveal much about the individual driving pattern. For example, an individual might show a high response at low frequencies and very little in the alpha region. In order to investigate further the pattern of one to one driving, the responses for each person in the ranges 3 to 4.5 c.p.s., 5 to 7 c.p.s., 8 to 13.5 c.p.s., 15 to 22 c.p.s., and 24.5 to 33 c.p.s., were summed separately and averaged yielding a profile of the activity in five frequency ranges. Since these values were highly skewed over the sample, a square-root transformation was used

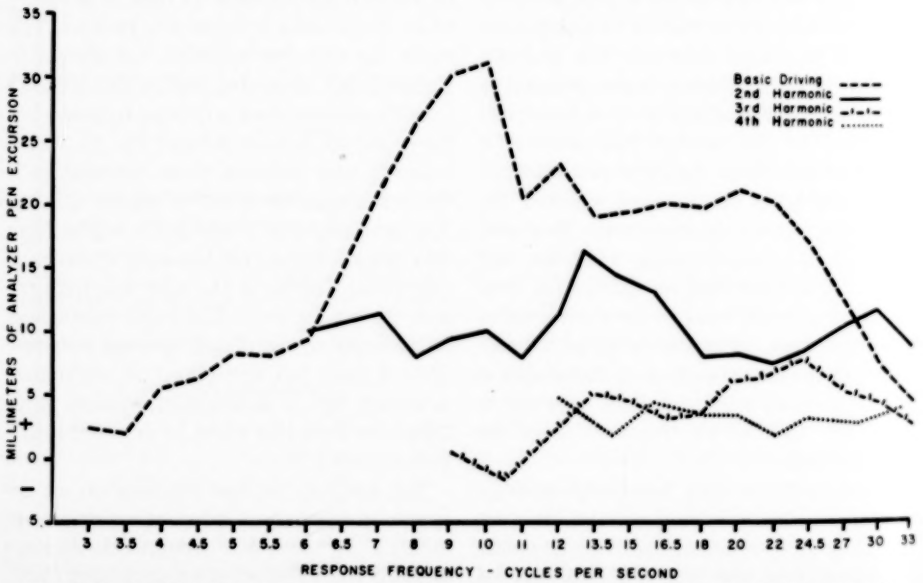

FIG. 1. Basic and harmonic median driving response at each frequency for the total sample (N = 171).

($\sqrt{x + 5}$) to obtain the inter-correlations. The matrix of intercorrelations is presented in Table 2. It may be noted that adjacent regions, with the exception of the 8 to 13.5 and 15 to 22 c.p.s. regions, are highly correlated, whereas none of the other correlations differ significantly from zero. Thus knowing that an individual drives relatively high in the alpha range indicates nothing about his driving in the low or high frequency ranges and relatively little about his driving in the range from 15 to 22 c.p.s., although it is likely that he also drives fairly well in the range from 5–7.5 c.p.s. The low correlation between the alpha and beta ranges was not too surprising since review of the individual records had suggested that most people had maximum driving in one or the other range rather than in both.

Using the profile of driving in the five frequency bands indicated above, all 171 individuals were categorized according to the region or regions in which they showed maximum driving. The criterion used was that the activity be at least 50 percent higher than that in the remaining regions. It was found that 54 individuals or 31.6 per cent drive distinctly more in the 8 to 13.5 c.p.s range; 21 or 12.9 per cent in the 15 to 22 c.p.s. range; while 19 or 11.1 per cent drive about equally in both ranges. For the remaining 45 per cent of the profiles, 10 per cent drove about equally in the three ranges 5 to 7, 8 to 13.5 and 15 to 22; 7 per cent in the ranges 5 to 7 and 8 to 13.5; 5.3 per cent in the ranges from 8 to 33 c.p.s.; 5.3 per cent from 5 to 33 c.p.s. and 4.1 per cent in the range from 15 to 33 c.p.s. The remaining profiles were of various miscellaneous types.

As the exact relationship of photic driving to spontaneous cortical activity was still in question (13, 15), the relationship between resting and driving activity was investigated for 120 subjects. Both eyes closed resting and eyes open resting activity were compared with photic driving with eyes open. These data are presented in Table 3. The results of these analyses revealed that the amount of spontaneous activity at a given frequency has little relationship to the amount of driving at that frequency.

TABLE 2

Intercorrelations of Average One-to-One Driving in Five Frequency Ranges (N = 80)

	3–4.5 c.p.s.	5–7 c.p.s.	8–13.5 c.p.s.	15–22 c.p.s.	24.5–33 c.p.s.
3 to 4.5 c.p.s.		0.53	0.14	0.06	0.12
5 to 7 c.p.s.			0.50	0.20	0.00
8 to 13.5 c.p.s.				0.24	0.08
15 to 22 c.p.s.					0.54

TABLE 3

Relationship of Resting EEG Record to Driving

Frequency Bands	Driving vs. Resting Eyes Closed*	Driving vs. Resting Eyes Open†
Total activity	0.10	0.26
3 to 4.5	0.28	0.24
5 to 7	0.12	0.21
8 to 12	0.07	0.23
13.5 to 20	0.07	0.19
22 to 33	0.02	0.04

* Pearson correlation N = 120.
† Rho correlation N = 40.

As our driving scores were based on activity evoked during photic stimulation minus activity during the eyes open resting period, the question was raised whether this was not equivalent to subtracting a constant which, if left in, might account for the reported correlations between spontaneous activity and photic driving. We re-analyzed our data and found that if the spontaneous activity was not subtracted from activity during photic stimulation, there was a low but significant positive relationship between the two measures ($r = 0.39$). The correlation was higher if both resting activity and activity during photic stimulation were recorded with eyes closed ($r = 0.62$). Thus when one subtracts the resting pattern from activity during photic stimulation, he is no longer able to predict from the amount of activity seen in the basic EEG the amount of driving that will occur.

Of particular interest was the significant

negative correlation -0.55 N = 16, when a comparison was made of resting EEG activity in the alpha region with eyes closed and driving in the alpha region with eyes closed. That is when resting EEG activity in the alpha region was subtracted from activity during photic stimulation a negative relationship existed between the amount of driving and amount of resting EEG activity. This negative relationship suggests an upper limit of cortical responsivity. Thus when there is a large amount of resting alpha activity you will get little increase due to photic stimulation, but conversely when there is little resting alpha activity there will be room for greater response to photic stimulation.

Our study was concerned not only with the pattern of driving but also with the stability of these patterns over time. An estimation of the relationship for each subject was obtained by use of an intraclass correlation technique outlined by Ebel (3). For the 47 subjects examined over three trials, records being taken over a nine month period, the range of intraclass correlations was from minus 0.23 to plus 0.86 with a median r of 0.49. Five of the intraclass correlations were not significant. As in other measures of photic driving, marked individual differences also are found here. Some individuals' driving profiles are highly stable from trial to trial while others are very unstable.

In Figure 2 are presented the median driving responses of the three trials. As can be seen the shapes of the profiles are quite similar even though they differ as to height. Thus when the individual variability is eliminated the shape of the driving profile for the group is highly similar from trial to trial.

While we have found that the shape of the driving profile was definable and consistent over a period of time, the amount of total driving and driving at most frequencies varied significantly for both groups and individuals from trial to trial. While we are unable at this time to offer an adequate ex-

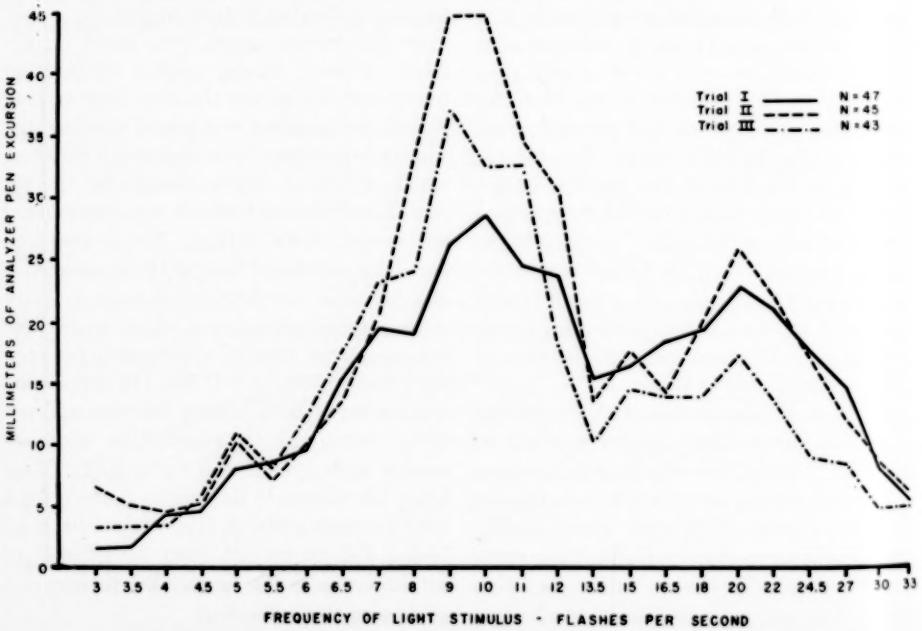

FIG. 2. Stability of photic driving. Median driving responses of three trials.

planation for the variability in amount of driving from trial to trial it is of interest that the lowest amount of activity was found in the initial record. Previous work from this laboratory suggested that tension serves to lower the driving response (20). It would seem likely that these subjects were most anxious during their first exposure to photic stimulation in a strange laboratory setting.

B. QUANTIFICATION AND DISTRIBUTION OF PHOTIC ACTIVATION

In addition to a quantitative measure of photic driving, a qualitative evaluation of the amount, degree and types of activation patterns was secured on the above sample plus a second rerun for the total sample. Analysis of photic activation in this section is based on the initial record of the total sample N = 182, and a second record on the total group remaining in the second year, N = 159. Forty-four subjects examined nine times over the three-year period will be reported in section D. Drop outs were due to change of vocational interest or scholastic reasons.

It is of obvious importance to clearly and as objectively as possible define what is meant by "photic activation" of the EEG. When the present research project was planned we spoke strictly in terms of the production of "paroxysmal" patterns, and in our initial study of the data one of us classified the records as paroxysmal, questionably paroxysmal, or nonparoxysmal. As further observations were made, a number of subjects were seen to have their records altered in such manner as to give a degree of irregularity that suggested "paroxysmal activity" yet was not exactly one of the seizure patterns seen in persons with epilepsy. Phenomena at first considered of possible clinical significance later were felt to be only complex rhythmical patterns resulting from a following of the light by brain potentials. Apparently other laboratories have encountered similar difficulties in classification as, for example, Schwab (16) called abnormal any response in which driving apparently spread from the occipital lead and was at double the amplitude of the resting pattern. A review of the literature (22) revealed that the flicker-Metrazol endpoint was similarly difficult to delineate and was defined differently by several separate laboratories.

With such consideration in mind, and following repeated examination of our own data, we attempted to code our records according to the criteria shown in Table 4. A rating of 1 (no activation) to 5 (extreme irregularity, paroxysmal) was given for each of 24 stimulation frequencies making a total of 24 ratings for each record. These criteria have been used by two electroencephalographically experienced raters who made 912 ratings of individual stimulus exposures (38 subjects, 24 frequencies each) and obtained an inter-rater reliability of 81 per cent. Few ratings differed more than one point and these were usually in the middle of the scale. On rerating the judgments of 288 ratings (12 subjects) the individual raters had a reliability with themselves of 86 per cent and 88 per cent. These re-ratings were separated by a period of at least two months and by the rating of at least 40 other records. Thus it appears that the scale is of sufficient objectivity to reliably assess the records taken during repeated photic stimulation experiments.

On the basis of the number of 1, 2, 3, 4, or 5 ratings received a procedure was devised which would allow each record to be placed into one of four categories: no activation, moderate activation, marked activation, and extreme activation (paroxysmal). In addition this procedure had to lend itself to easy statistical manipulation, and allow for full use of all 24 ratings. Simple weighting of each of the five points on the scale was not possible as the scale is not an equidistant interval scale. That is, a single five rating is felt clinically to be indicative of a marked paroxysmal record while 12 three ratings are felt to be necessary before a subject's record

TABLE 4

Classification of "Activation" Patterns Induced by Intermittent Photic Stimulation

1. *No irregularity*
   Classify as regular those sections:
   (a) In which groups of waves of similar amplitude and frequency occur in trains without marked changes between.
   (b) Those sections in which groups of waves of slightly dissimilar (1 or 2 units) frequency occur for major part of record.
2. *Slight irregularity*
   To classify a section as slightly irregular consider the following:
   (a) No persistent clearly defined frequency is observable, or several different countable frequencies of greater than 1 to 2 unit change are seen.
   (b) The wave forms are of moderate complexity, some sine configurations are seen.
3. *Moderate irregularity*
   To classify a section as moderately irregular consider the following:
   (a) Predominantly non-sine wave configurations are seen.
   (b) Subsequent waves are generally dissimilar in frequency and amplitude from the preceding waves.
   (c) Sharp changes in amplitude are seen.
4. *Marked irregularity*
   Classify as markedly irregular those sections in which waves of at least 100 μv are seen, at least twice the background activity. At least one definite classically abnormal wave pattern is seen.
5. *Extreme irregularity*
   Classify as extremely irregular those sections in which classically abnormal or paroxysmal wave forms are seen for at least one second's duration. The extremely disturbed activity is over four times the background activity or over 150 μv.

General Considerations:

1. In the situation in which a flicker frequency is repeated or two or more classifications might be identifiable within a 40-second strip at a given frequency, the highest rating will be assigned.
2. "Classically abnormal wave patterns" in 4 and 5 are defined as spike and wave, single spike, successive spikes, etc.
3. The situation in which alpha patterns come and go will ordinarily be classified as regular if alpha persists over the major part of the strip.

could be classified as questionable. Any weighting system, therefore, must weight each step on the rating scale according to its clinical significance. A geometric weighting system with a base of three in which a rating of one is given a weight of 1; a two rating a weight of 3, a three rating a weight of 9, a four rating a weight of 27 and a rating of five a weight of 81 seemed appropriate. Work to date indicates that such a weighting system is indeed feasible. The reliability between the two raters for 38 records computed from weighted scores is 0.85. That the weighted scores adequately reflect the clinical evaluation of the records is indicated by the mean weighted score of 82.0, for those classified as no activation by clinical evaluation, 177.6, for the moderate activation group, 235 for the marked activation, and a mean weighted score of 429.6 for the marked paroxysmal group. The range of scores found to date is from 50 to 930 with skewing toward the low end of the distribution. This skewing would be expected as the predominant response is no or slight activation to photic stimulation.

All analyses of pattern and stability of photic activation and the relationship of photic activation to other variables are based on these weighted scores. From the distribution of scores and clinical evaluation the following cutting points were used for dividing the subjects into the four activation groups; 24 to 139 no activation, 140 to 209 moderate activation, 210 to 279 marked activation, and a weighted score of 280 or above was classified as extreme activation (paroxysmal).

Before presenting the distribution of activation patterns, of interest is the distribution of 1, 2, 3, 4 and 5 ratings over each of the 24 flicker frequencies. This distribution is graphically presented in Figure 3. As 1 and 2 ratings occurred in equal number at all frequencies and indicate no or only slight activation they were not plotted. Three and four ratings can also occur at any frequency but marked activation (4 ratings) are most often found above 8 c.p.s. Extreme activation (5 ratings) were never found below 11 c.p.s. with the majority occurring at 13.5 and 15 c.p.s.

In Table 5 is the distribution of activation patterns for the original and repeat records

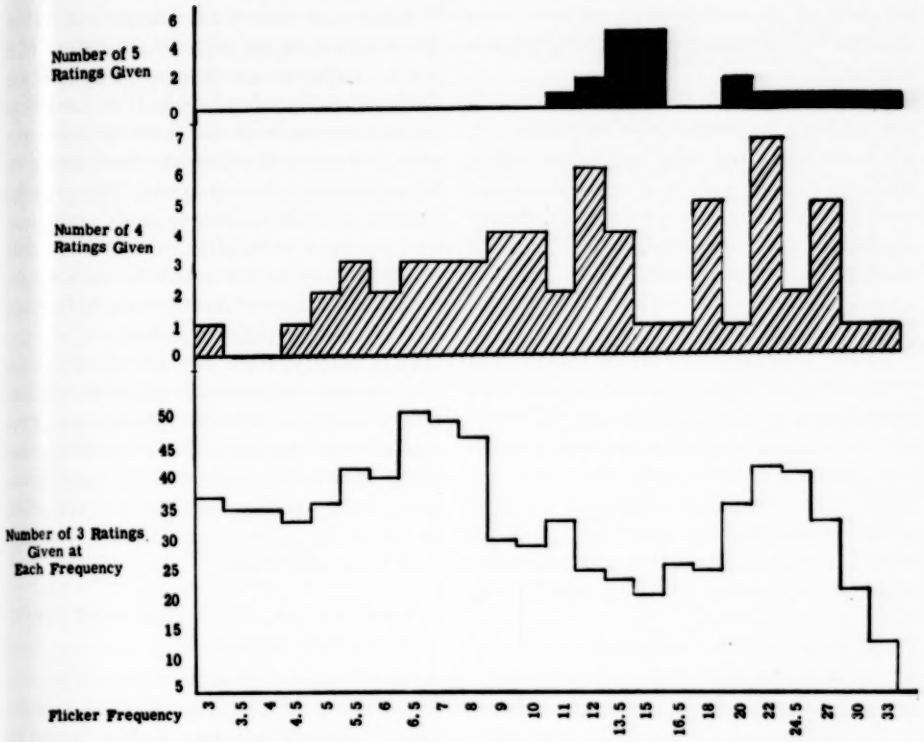

FIG. 3. Distribution of activation ratings at each frequency for 3-4-5 values (N = 181).

for the total sample. The distribution of activation patterns for the two records is highly similar with the majority of the subjects showing no activation and only a small percentage showing marked or extreme activation. These findings are very similar to those of Mundy-Castle (13). Using a sample of 154 young normal adults, mean age 22 years, he reported only six (3.9 per cent) abnormal records and five (3.25 per cent) questionable records. The records he rated as abnormal all displayed typical polyspike or wave spike epileptic characteristics, accompanied either by violent myoclonic jerks or slight twitches of the upper extremities and face or eyes in all but one subject.

TABLE 5
Distribution of Photic Activation Patterns

	N	Per cent
Type of activation record one (N = 182)		
No activation	142	78.0
Moderate activation	24	13.2
Marked activation	8	4.4
Extreme (paroxysmal) activation	8	4.4
Record two (N = 159)		
No activation	125	78.6
Moderate activation	25	15.7
Marked activation	2	1.3
Extreme (paroxysmal) activation	7	4.4

C. STABILITY OF PHOTIC ACTIVATION

Before any measure, psychologic or physiologic, can be used as a reference dimension to relate to other variables its stability over time, (reliability) must first be examined. If it remains consistent over time than any single measure may be taken as representative and used as a reference dimension. If found to fluctuate from record to record, then the important question becomes is this fluctuation logically related to changes in

the subject or environment or are these changes due to chance and seemingly unexplainable.

Stability of activation patterns for the 159 subjects seen twice was examined by: (1) correlating the total activation scores obtained by each subject on records one and two; (2) by tabulating the subjects who remained in the same category, *i.e.*, no activation, moderate activation, etc., on both records; and (3) by noting the types of shifts that occurred.

As the distribution of scores was skewed toward the no activation end, square root transformation was obtained and the Pearson correlation coefficient between records one and two was obtained from these log scores. This correlation coefficient was 0.69 which is statistically significant (beyond 0.01) from zero. Thus in this group, response to photic activation is highly stable from one record to another.

Examination of the individual records revealed a similar high degree of consistency. From Table 6 it can be seen that 75.4 per cent of the subjects remain in the same category on both records. The greatest stability is in the no activation and extreme activation groups. Of the 216 records classified as no activation on either one or both records, 87.4 per cent showed no change, and of the 13 records showing extreme activation 61.5 per cent showed no change. Only 32.7 per cent of 49 records classified as moderate activators remained the same on both records. No marked activators were found to be consistent on both trials. The greatest number of changes were from no activation to moderate activation, only 5 records changed from no activation to marked activation and but one record changed from no activation to extreme activation.

TABLE 6

Distribution and Types of Change of Photic Activation over Two Records (N = 159)

	N	Per cent
Subjects showing		
No activation both trials	108	67.9
Moderate activation both trials	8	5.0
Marked activation both trials	0	—
Extreme (paroxysmal) activation both trials	4	2.5
Types of change		
No activation to moderate*	25	15.1
No activation to marked	5	3.1
No activation to extreme	1	.6
Moderate activation to marked	4	2.5
Moderate activation to extreme	2	1.3
Marked activation to extreme	2	1.3

* Change not necessarily always from trial 1 to trial 2. Indicates type of change only.

In summary, most subjects show no activation response to photic stimulation while only a small per cent (4.4) show a paroxysmal cortical response. Both responses are fairly consistent with the no activation group being most stable. Records classified as indicating moderate or marked activation tend to be least stable.

D. STABILITY OF ACTIVATION OVER THREE YEARS, NINE RECORDS

As indicated earlier, 50 subjects were followed over a three year period. Nine records, taken three months apart, were obtained on these subjects. The degree of relationship among the nine trials was estimated by use of an intraclass correlation coefficient computed from the activation score for each record. This correlation was 0.85 which indicates a high degree of consistency over the nine records for this group. This stability is further illustrated in Table 7 which indicates that 50.0 per cent of the records were placed in the same activation category on seven or more of the nine trials. No subject's record showed more than 5 shifts over the nine trials.

In Table 8 are listed the types of changes from one trial to another. Again those records classified as showing no activation are found to be the most stable. One subject's record was classified as an extreme activator on eight of the records and a marked activation on the ninth. Among the other individuals there was considerable shifting from category to category. In four subjects, shifts

occurred from no activation to a paroxysmal response. An example of such an unstable record is presented in Figure 4.

When the mean scores for the nine trials are examined in Table 9, an interesting, but as yet unexplainable, trend is noticed. The mean scores for trials one, four and seven are lower than the other six. These three trials are the first trial of each school year and while record 7 is the only one significantly different t = 2.69, from the last record of the year the trend is unmistakable. The same factors that worked to reduce the amount of photic driving on record one may be operating here. However, if this be tension and situational anxiety it should have disappeared by the third year and after six similar records.

E. RELATION OF PHOTIC DRIVING AND PHOTIC ACTIVATION TO OTHER VARIABLES

To gain further understanding of the cortical response to photic stimulation, photic driving and activation were related to resting EEG classification, psychiatric and neurological history and examination, certain physiological variables, and a battery of psychological tests which purport to measure feelings of dysphoria or anxiety. In addition to this relatively psychologically homogeneous sample of graduate students, photic driving and activation were also investigated in a carefully selected psychiatric sample.

1. Relation to resting EEG. The total amount of photic driving over the 24 frequencies was computed for subjects with normal resting EEG records, N = 148, and for those with other than normal records, N = 34. The resting records were read by a certified electroencephalographer. The mean driving scores for the two groups were 413.6 and 380.6 respectively. Difference between the two are not significant t = 0.86.

Like Mundy-Castle (13) we also found no relationship of degree or types of photic activation to resting EEG. The number of each type of activation pattern occurring in various resting EEG classifications is presented in Table 10. Resting normal records may show extreme paroxysmal response to flicker and paroxysmal resting records may show no deviant response to flicker. The resting EEG was also given a rating of 1, 2, 3, 4 or 5 using the same scale used for classifying the activation response. There was no resting rating greater than 3 and there was no relationship of the resting EEG rating to the ratings given to the EEG activity during flicker. Thus the resting EEG does not seem to be an important predictor of response to flicker.

2. Relation to psychiatric and neurologic history and examination. The 50 subjects being followed over the three-year period were given a thorough neurologic and psychiatric examination by a neuropsychiatrist certified by the Board in both specialties. Because of the nature of the sample no gross

TABLE 7

Stability of Activation over Three Years, Nine Records (N = 44)

	N	Per cent
Same category 9 trials*	12*	27.3
Same category 8 trials†	8†	18.2
Same category 7 trials	2	4.5
Same category 6 trials	6	13.6
Same category 5 trials	9	20.4
Same category 4 trials	7	15.9

* All classified as no activation.

† One classified extreme activation, 7 no activation.

TABLE 8

Types of Changes over Three Years, 9 Records (N = 44)

Type of Change	N	Per cent
No change*	12	27.3
No activation to moderate†	11	25.0
No activation to marked	14	31.8
No activation to extreme	4	9.1
Moderate to marked	2	4.5
Moderate to extreme	1	2.3

* All classified as no activation.

† Indicates that one or more of the nine records were classified as a non-activator and one or more as a moderate activator.

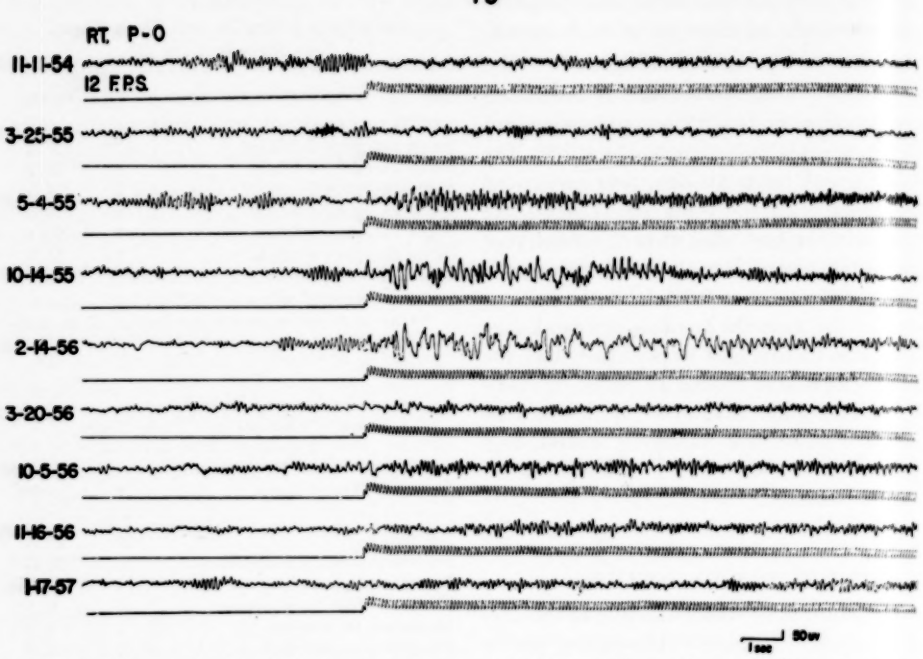

FIG. 4. Right parietal-occipital tracing of response at 12 f.p.s. illustrating variability of response or one subject over three-year period, nine records.

TABLE 9

Photic Activation Score Means, and Standard Deviation for Each of Nine Records (N = 44)

Trials	Mean	Standard Deviation
1*	122.1	88.3
2	154.5	126.0
3	165.1	143.4
4*	122.0	94.1
5	144.8	116.6
6	145.7	87.8
7*	108.9	66.2
8	132.1	83.7
9	146.6	71.5

* First record of each school year.

TABLE 10

Relationship of Basic EEG Classification and Photic Activation

EEG Classification	No Activation	Moderate Activation	Marked Activation	Extreme Activation
Normal (N = 148)	119	19	6	4
S_1 (N = 11)	8	1	—	2
S_2 (N = 2)	2	—	—	—
F_1 (N = 2)	2	—	—	—
Paroxysmal (N = 5)	2	—	1	2
Mixed fast slow (N = 9)	6	2	1	—
Low voltage fast (N = 5)	3	2	—	—

neurologic or psychiatric pathology was found. Thus the negative findings of no relation of photic activation to history of mild concussion, migraine and headaches does not answer the question of what would be the response to photic stimulation in patients with gross brain damage or dysfunction. One subject with hereditary nystagmus and tremor had the highest activation score of the total group, 930, indicating a paroxysmal response. This response was very consistent over the 9 trials only once dropping to

"marked activation." Mundy-Castle (14) did not include any organics in his study but reports that marked abnormalities have been evoked in isolated cases of suspected pituitary tumor, diffuse degeneration of the brain, and cerebral arteriosclerosis probably involving basal structures. Kooi (10), in a study of 100 brain-damaged patients, found a reduced responsiveness to photic stimulation, broad triphasic response to slow rates of stimulation and infrequent myoclonic responses.

In our group there was no relation of activation to a family history of "nervousness" or the presence in the subject of what was labeled "mild anxiety."

3. Relation to psychologic tests. The Cornell Medical Index, Cornell Word Form, Taylor Anxiety Scale, Depressed Affect Scale, and Annoyance Test were given to each of the subjects at each repeat EEG examination for the first five records of the study. These test scores were transformed to standard scores with a constant of 10 added to eliminate negative values. A composite anxiety score based on the records over the five trials was computed for each subject. The scores were computed so that a composite score of 10 or above indicated above average anxiety and a score below 10 indicated below average anxiety with reference to the total group.

Total photic driving, amount of driving in the 5 frequency bands (3 to 4.5, 5 to 7, 8 to 12, 13.5 to 20, 22 to 33), stability of driving, photic activation and stability of photic activation were compared for the 10 most anxious and 10 least anxious subjects based on the psychology test scores. No differences between the most anxious and least anxious subjects were found for any of the driving or activation measures. Anxiety, as measured by these tests, is not related to response to photic stimulation.

Resting blood pressure and pulse rate were not related to photic activation nor were there any significant changes in these two measures during flicker.

F. RESPONSE TO FLICKER IN A PSYCHIATRIC SAMPLE

As part of a larger study of schizophrenia 30 carefully chosen (3 of 4 psychiatrists had to agree on the diagnosis) schizophrenics and 23 nonschizophrenics (primarily neurotics and sociopaths) were examined using the same procedures. Patients with head injury or with a history of seizures were excluded. Photic activation records were available for both groups, but because of recording difficulties photic driving data was available for only 18 of the schizophrenics and 10 nonschizophrenics.

Both the schizophrenic and nonschizophrenic samples showed more marked or extreme activation during flicker than did the seminary sample. Seven (23.3 per cent) schizophrenic patients, and 6 (26.1 per cent) nonschizophrenic patients had marked or extreme activation responses while only 16 (8.8 per cent) of the graduate students had marked or extreme responses. The difference between the students and patients is significant beyond the 0.05 level, $t = 2.53$. As the students were not comparable with respect to age, socio-economic status or IQ, no definitive claims are made. However, the differences with respect to these variables will probably be found wanting as an explanation of the cause for the greater activation response in the psychiatric group.

There was no difference between the psychiatric and student groups with respect to 1:1 photic driving or second or third harmonic driving response.

There have been many reports that activation by flicker was indicative of a low convulsive threshold and patients with a history of seizures have tended to show more abnormal responses to flicker than a control group (6, 14). As the convulsive threshold for each of our psychiatric patients was carefully measured by a technique developed in our laboratory (22), it was possible to relate the activation response to flicker with convulsive threshold. As the convulsive

threshold and activation response to flicker did not differ significantly for the schizophrenic and non-schizophrenic group, comparison of activation and convulsive threshold is based on the combined psychiatric sample. Chi square analysis based on 45 patients for which both threshold and activation scores were available indicated a significant negative relationship between the two measures ($X^2 7.5$, contingency coefficient $-$ 0.38, p. 0.01). Patients with a low convulsive threshold showed significantly more activation to flicker. These results support the belief that marked or extreme activation to flicker are related to a low convulsive threshold.

DISCUSSION

The above investigation utilizing an electronic EEG analyzer has presented a clearer picture of the EEG reaction to photic stimulation than heretofore available. First as regards the EEG driving response to photic stimulation, it has been clearly shown that in this sample photic driving is a universal phenomenon. The peak response is usually in the alpha region and although this would seem to imply that the amount of activation at any driving frequency is directly related to the amount of activity in the resting record, such is actually not the case. Earlier studies to this effect may have been so interpreted as a result of failure to subtract the resting activity from the total activity seen during the period of photic stimulation.

It was noted that the greatest amount of both driving and activation occurred in the range above 9 c.p.s. A clear explanation for this is not available but Gastaut (5) states that flashes of 15 to 20 c.p.s. fall primarily in the period of facilitation and hence serve to recruit new neural units to activity.

Our results seem to suggest that activity induced by photic stimulation is not simply an augmentation of brain activity seen at rest, but rather may bring into play brain units not usually functioning to produce the eyes open resting electroencephalogram. In a few cases seen in our laboratory however, and from data presented by Brazier (1) it has been shown possible, by photic stimulation, to apparently increase the activity at a certain frequency at the expense of reducing activity in an adjacent frequency. This would imply the ability of neural units to shift their frequency response. Our data from photic stimulation with eyes closed suggests, in addition, that there is an upper limit of cortical responsitivity beyond which individual neuron units cannot respond. Such individual modes of brain response to light stimulus must certainly reflect characteristic patterns of brain organization which may well relate to behavioral patterns and suggest that photic driving may well add a new parameter to EEG investigation that warrants further study regarding psychologic or physiologic correlations.

Fluctuations in the amount of driving response were clearly evident in many subjects followed at three month intervals. Our failure to find obvious relationships with gross psychologic or physiologic variables leave, still open, the question of possible correlations. Although Shagass was able to relate such quantitative changes to day to day fluctuations in mood of psychiatric patients, introspective observations from our students, not in therapy, failed to show such relationship. It is of course possible that more sensitive personality measures would have confirmed Shagass' findings.

Similar fluctuations of the activation response are even more puzzling for the sporadic occurrence of photic induced deviant EEG activity in this effectively functioning and healthy group is difficult to explain in terms of the usual view of such cortical dysfunction as being indicative of brain pathology. In only the one control subject with signs of hereditary brain disorder was marked or extreme activation apparent throughout the nine records. On the other hand six other control subjects showed

about as much activation in more than 50 per cent of their nine records and yet had no sign, symptom or history of either psychiatric or neurologic disease to correlate with such activation. As Hill (7) has earlier pointed out the significance of a single EEG record, even an activated one, is certainly open to considerable question. In one individual previously reported (24) changes in blood sugar and the amount of sleep seemed to combine to increase the cortical sensitivity to flickering light. This, however, was not true in other instances, nor could any obvious variation in these subjects' statements regarding shifts in their emotional state (*i.e.*, well being, dysphoria or anxiety) be related to such findings. That photic activation may have an as yet unexplained clinical importance however, is suggested by the increased occurrence of marked and extreme activation in our psychiatric sample where a 24.5 per cent figure of activation was found to significantly relate to low convulsive threshold. Gastaut's opinion (4) that this reactivity points to diencephalic disorder in such patients however, still requires further evidence.

CONCLUSIONS

Patterns, stability and correlates of photic EEG activation were studied in 182 young adult males and 53 psychiatric patients with the following findings:

1. Photic driving is a universal phenomenon with peak response in the alpha range.

2. The shape of the driving profile remains relatively stable over time but the amount of driving at each frequency tends to fluctuate.

3. Marked or extreme photic activation occurred in 8.8 per cent of a healthy young adult group but occurred in 24.5 per cent of a psychiatric population.

4. Paroxysmal activation is rare with stimulation below 10 c.p.s.

5. On nine occasions over a period of three years marked shifts occurred in some subjects in the amount of photic activation.

6. In the control group neither photic driving, photic activation nor changes in photic activation were found to relate significantly to resting EEG pattern, changes in pulse or blood pressure, self-evaluation of psychologic state or of positive items in personal or family neuropsychiatric history.

7. There was no difference between schizophrenic and nonschizophrenic psychiatric patients in reference to photic activation but in both groups a low convulsive threshold was significantly related to marked EEG activation.

REFERENCES

1. Brazier, M. A. B. ERDL Symposium on Photic Stimulation, Tulane University, New Orleans, 1957.
2. Chamberlain, G. N. A. and Gordon-Russel, J. Electroencephalog. & Clin. Neurophysiol., **5**: 169–175, 1953.
3. Ebel, R. L. Psychometrika, **16**: 407–424, 1951.
4. Gastaut, H. Electroencephalog. & Clin. Neurophysiol., **2**: 249–261, 1950.
5. Gastaut, H. Electroencephalog. & Clin. Neurophysiol., **3**: 87–88, 1951.
6. Herrlin, K. M. Electroencephalog. & Clin. Neurophysiol., **6**: 573–589, 1954.
7. Hill, D. J. Ment. Sc. **102**: 264–271, 1956.
8. Hoenig, J. and Lieberman, D. M. J. Neurol. Neurosurg. & Psychiat., **16**: 30–34, 1953.
9. Johnson, L. C., Ulett, G. A. and Gleser, G. USAF School of Aviation Medicine Report. 57–54.
10. Kooi, K. A., Eckman, G. H. and Thomas, M. H. Electroencephalog. & Clin. Neurophysiol., **9**: 239–250, 1957.
11. Lieberman, D. M., Hoenig, J., and Hacker, M. Electroencephalog. & Clin. Neurophysiol., **9**: 9–18, 1954.
12. Leffman, H. and Perlo, V. P. Electroencephalog. & Clin. Neurophysiol., **7**: 61–66, 1955.
13. Mundy-Castle, A. C. Electroencephalog. & Clin. Neurophysiol., **5**: 1–22, 1953.
14. Mundy-Castle, A. C. Electroencephalog. & Clin. Neurophysiol., **5**: 187–202, 1953.
15. Ostow, M. Electroencephalog. & Clin. Neurophysiol., **1**: 245, 1949.
16. Schwab, R. S., England, A. C., Jr. and Gray, N. M. Electroencephalog. & Clin. Neurophysiol., **7**: 464–465, 1955.
17. Shagass, C. Electroencephalog. & Clin. Neurophysiol., **6**: 445–453, 1954.
18. Shagass, C. Amer. J. Psychiat., **112**: 41–46, 1955.
19. Smith, K., Ulett, G. A. and Johnson, L. C.

A. M. A. Arch. Neurol. & Psychiat., **77:** 528–532, 1957.

20. Ulett, G. A. and Gleser, G. Science, **115:** 678–682, 1952.
21. Ulett, G. A., Gleser, G., Winokur, G. and Lawler, M. A. Electroencephalog. & Clin. Neurophysiol., **5:** 23–32, 1953.
22. Ulett, G. A., Brockman, J. C., Gleser, G. and Johnson, A. Electroencephalog. & Clin. Neurophysiol., **7:** 597–607, 1955.
23. Ulett, G. A. and Loeffel, R. G. Electroencephalog. & Clin. Neurophysiol., **5:** 113–115, 1953.
24. Ulett, G. A. Am. J. Psychiat. **114:** 127–133, 1957.
25. Walter, W. G. J. Ment. Sc., **96:** 1–31, 1950.

GLUTAMIC OXALACETIC TRANSAMINASE IN CEREBROSPINAL FLUID

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Serum glutamic oxalacetic transaminase (GOT) determination has become widely accepted as a help for diagnosis in myocardial infarction and acute liver diseases. Originally, Cohen (3) showed the distribution of this enzyme in different tissues, large amounts being present in heart muscle, skeletal muscle, brain and liver. The same pattern of distribution of this enzyme was confirmed by Awapara (1). Because of the tedious and inaccurate methods of determination this was not utilized in clinical medicine until Karmen *et al.* (6) devised a simple, accurate and reproducible spectrophotometric method. LaDue and Wroblewski (7, 12), on examining serum GOT in cerebrovascular disease and degenerative diseases of the central nervous system, found no significant changes. Wakim and Fleisher, however, in experimental brain infarction in dogs (11), noted significant elevation of serum GOT. Recently, Fleisher, Wakim and Goldstein (4) and this author (10) found similar alterations in patients with cerebral vascular accidents.

Because of the interference of the blood-brain barrier, the examination of GOT in cerebrospinal fluid appears to be of more significance than that of serum GOT in diseases of the central nervous system. The action of the blood-brain barrier in efficiently preventing interchange of this enzyme between the central nervous system and serum has been clearly demonstrated (10). Serum elevations of GOT in cerebrovascular disease are dependent, therefore, on a rather widespread disruption of the blood-brain barrier and so cannot detect small infarctions. This report is intended to present further observations concerning GOT activity in central nervous system diseases and to attempt to define more clearly the clinical usefulness of this determination in cerebrospinal fluid.

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METHODS

The spectrophotometric method outlined by Karmen (6) was used. This is an indirect measurement of transaminase since the method actually determines the rate of oxidation of reduced diphosphopyridine nucleotide. The steps of the reaction are as follows.

(1) aspartate + D-ketoglutarate $\xrightleftharpoons{\text{GOT}}$ oxalacetate + glutamate

(2) oxalacetate + reduced DPN $\xrightleftharpoons{\text{malic dehydrogenase}}$ malate + oxidized DPN

In Reaction 2 malic dehydrogenase works two ways, namely, facilitation of reaction and removal of oxalacetate, thus forcing the reaction to the right. Reduced DPN and malic dehydrogenase were kept frozen and fresh solutions of these substances were made for each determination. The other solutions were kept at 2° C. In the procedure, 0.05 ml. of 0.2 M aspartate solution (pH 7.5) is added to the specimen consisting of 0.1 to 0.5 ml. of cerebrospinal fluid, then 0.2 ml. of reduced DPN (1 mg. per ml.), 0.1 ml. of malic dehydrogenase (2000 units per ml.) and 1.9 ml. of 0.1 M phosphate buffer (pH 7.5) were added in that order. After this mixture, at least 10 minutes were allowed to pass for the reduced DPN and malic dehydrogenase to reach equilib-

rium. Finally, 0.2 ml. of 0.1 M D-ketoglutarate solution (pH 7.5) was added. The entire reaction mixture constitutes 3 ml. of solution. The determination was performed on a Beckman Model B. spectrophotometer by following this decrease in the absorbance at 340 mμ, the absorbance maximum of reduced DPN. All studies were performed at room temperature (25 to 26° C.) and the activity is expressed in "units." The unit is defined as the decrease in optical density of 0.001 per minute per ml. All specimens were kept frozen until the time of examination.

Specimens from 32 patients with acute cerebrovascular accidents were examined, among which were included patients with cerebral hemorrhage and subarachnoid hemorrhage. Thirteen cases of brain tumor were included, consisting of gliomas, meningiomas, third ventricle tumors and cerebral metastases. A specimen from one patient with subdural hematoma was tested. Four cases of pseudotumor cerebri were included. Because of the interesting result noted in a case of internal hydrocephalus in the first report by the author (10) four patients of external hydrocephalus were examined. Other patient groups included meningitis (7 bacterial, 4 viral), degenerative disease of the central nervous system (4 multiple sclerosis in exacerbation, 1 cerebellar degeneration, 1 Friedreich's ataxia), metabolic disease affecting the function of the central nervous system (3 hepatic coma, 1 diabetic coma, 1 uremic coma, 1 acute porphyria) and various types of other neurologic disorders including tabes dorsalis, organic psychosis, Parkinson's disease, trigeminal neuralgia, hypertensive encephalopathy and intervertebral disc protrusion. Observations made in patients with convulsive disorders previously reported were supplemented with specimens obtained during an interseizure period as well as during and immediately after grand mal seizures. Observations were also made on patients with petit mal and psychomotor seizures. The determinations of GOT activity in convulsive disorders were extended to include patients having electric shock therapy. Four patients were selected who had received electroshock treatments prior to the present determination and cerebrospinal fluid was taken just before and 20 and 30 minutes after an electroshock treatment. Transaminase activity of different parts of the human brain was measured.

RESULTS

The control value of cerebrospinal fluid GOT, as determined previously is 16.8 ± 7.6 units (2 to 30 units). If this value is expressed in terms of micromoles of oxalacetate produced per hour per ml. at 37° C. it corresponds to 0.84 ± 0.38 μmole per hour per ml. This figure is rather closer to the one reported by Fleisher, Wakim and Goldstein (4), which is 0.8999 ± 0.042 μmole per hour per ml. than that reported by Green *et al.* (5) which is 0.43 ± 0.2 μmole per hour per ml. This figure seems to be too low, as already pointed out by the former authors. The control value used in this investigation is derived from a population between the ages of 30 and 70 years. Because some patients, particularly those who presented hydrocephalus, were children, it is desirable to know the normal range of this young age group. However, as a practical problem it is difficult to obtain sufficient samples of this age group to provide reliable data. In order to obtain comparable values, however, some specimens from infant and child groups were tested. The value thus obtained fell within the normal range of the adult group. It seems safe to state that whenever a value found among this age group is higher than the normal adult maximum value, it should be considered abnormal.

The results found in cases of acute cerebrovascular accident are presented in Table 1. Among 32 patients tested, 19 showed a value above normal, of which 9 elevated unequivocally and 10 exhibited a borderline elevation. The unequivocal elevations

constitute 28 per cent of the total patients, a figure closely approximating that reported by Fleisher *et al.* (4). Some of the specimens examined were bloody. LaDue and Wroblewski (7) and, more recently, Green *et al.* (5) stated that hemolysis produces significant increase in GOT activity. Magalini and Stefanini (8) also reported GOT activity in platelets. An experiment *in vitro* was performed, mixing fresh blood with the spinal fluid of the same individual in various concentrations approximating those found in cerebral or subarachnoid hemorrhage (8). In serial determinations of specimens incubated at 37° C., the peak of GOT activity was found at around 24 to 48 hours, reaching, at most, somewhat over twice the original activity. Taking this into consideration, results presented in Table 1 would be accepted as recorded except for one instance (Case 8). The results of this study suggest that the GOT determinations of bloody spinal fluid are little affected by the blood, if the observations are made on centrifuged spinal fluid taken immediately after the bleeding or if the determinations were made on spinal fluid taken 3 days after the hemorrhage. If, however, all bloody specimens are excluded from consideration, the total number of patients is 25, among which 6 show a significant elevation, 8 are borderline and 11 reveal no elevation. The significant elevation thus constitutes 24 per cent.

Among 13 patients with brain tumor, 1 spinal fluid showed significant elevation and 2 were in the upper limits of normal. These 3 patients had obstructive hydrocephalus to some extent (Table 2). One case of congenital internal hydrocephalus showed a marked elevation of GOT, yet 4 cases of external hydrocephalus were within normal limits (Table 3). Four cases of pseudotumor cerebri showed normal levels of GOT.

Patients with convulsive disorders, as seen in Table 4, showed borderline to definite elevation only when the specimen was obtained during or soon after termination of a convulsion. One child (Case 7) whose specimen was obtained during a short interval between seizures during status epilepticus showed marked elevation. This child died of uncontrolled status epilepticus. The electroshock patients showed slight elevation after shock (Table 5). However, this small elevation can be explained as representing one brief seizure, whereas patients in status epilepticus who showed definite elevation above normal had a much longer period of convulsions.

Determinations were made on one case of hemiballismus. The GOT level was normal despite the presence of incessant violent movements which had been observed for several days. The normal values were obtained from the other neurologic disorders examined.

Table 6 shows distribution of GOT in various parts of a human brain which was removed approximately 8 hours after death in a patient who succumbed to carcinoma of the ascending colon with metastases to the liver, kidney, peritoneum and lung. Extraction was made in 0.25 M sucrose solution. Highest values were noted in the cerebellum followed by the pons. The values for the cerebral cortex and internal capsule were almost identical. The hypothalamus and thalamus provided the lowest figures. The observation made by others (2, 11) that the cerebral cortex contains more GOT than the white matter was not confirmed. The reason for this discrepancy is not clear but may merely reflect differences in methods of extraction and the time of examination after death.

In the recent attempts to apply GOT determinations to neurologic disorders there has been a hope that this could be as useful in this field as it has been in patients with myocardial infarction and hepatic disease. Recently, this author attempted some correlation between GOT levels and prognosis in acute cerebral vascular disease (10). Green *et al.* (5) have stated that there is a definite relation between the degree of ele-

TABLE 1

Cerebrospinal Fluid GOT Levels in Acute Cerebrovascular Accidents
(Expressed in units)*

Case No.	Clinical Diagnosis	Age	Sex	Day 1 (within 24 hr.)	Day 2 (within 48 hr.)	Day 3 (within 72 hr.)	Day 4 (within 96 hr.)	Day 5 (within 120 hr.)	Within 1 Week	Within 2 Weeks	Within 1 month	Prognosis
1	Thrombosis mid. cerebral artery	74	F				96		64	46		no change
2	Intracerebral hemorrhage	61	M						20 X	22 less X		improved
3	Thrombosis basilar artery	84	F			39			56 X			died
4	Thrombosis mid. cerebral artery	74	M		14			16				improved
5	Thrombosis mid. cerebral artery secondary polycythemia	61	M		32	23						improved
6	Intracerebral hemorrhage	70	M	50 bloody, slight X (RBC 51,600)			4 increased X (RBC 13,240)					died
7	Thrombosis mid. cerebral artery	54	M	20			30					died
8	Intraventricular hemorrhage	56	M	94 bloody marked X								died
9	Thrombosis mid. cerebral artery	72	F	24			44					died
10	Thrombosis basilar artery	70	F	32		160						died
11	Thrombosis mid. cerebral artery	56			20		8					improved
12	Thrombosis basilar artery	70	M		26		10					died
13	Thrombosis mid. cerebral artery	67	F						22	12		died
14	Subarachnoid hemorrhage	50	M	14 bloody, slight X			14 increased X					improved
15	Thrombosis basilar artery	47	M	74		92 slight X				12		improved
16	Embolism mid. cerebral artery	82	M	30					24			improved
17	Thrombosis mid. cerberal artery	60	M	20								died
18	Thrombosis mid. cerebral artery	78	M	28		44 faint X						died
19	Thrombosis mid. cerebral artery	55	M	8		6						improved
20	Intracerebral hemorrhage	46	M		30 X							improved
21	Thrombosis mid. cerebral artery	67	M	10				34		10		no change
22	Thrombosis basilar artery	49	F	20			10					died
23	Thrombosis mid. cerebral artery	62	F	20								improved
24	Subarachnoid hemorrhage	73								34 still bloody (RBC 60,000)		improved
25	Subarachnoid hemorrhage	72	M		50 slight X			46 increased X				died
26	Thrombosis mid. cerebral artery	78	F	30								died
27	Thrombosis mid. cerebral artery (1 side, old cerebral vascular accident other side)	73	M	14			10				10	no change
28	Thrombosis mid. cerebral artery	75	F		24			22				improved
29	Intracerebral hemorrhage	57	F			32						improved
30	Subarachnoid hemorrhage	49	M	30 grossly bloody, slight X								died
31	Intracerebral hemorrhage	33	F		22 slight X (RBC 6000)							improved
32	Thrombosis internal carotid artery	52	M	18			30					died

* X, xanthochromia.

TABLE 2

Brain Tumor

No.	Diagnosis	GOT
		units
1	Astrocytoma	10
2	Astrocytoma	16
3	Astroblastoma	22
4	Astroblastoma	14
5	Astrocytoma	12
6	Astrocytoma	10
7	Glioblastoma multiforme	10
8	Medulloblastoma with obstructive hydrocephalus	30
9	Meningioma	18
10	Metastatic carcinoma	20
11	Astrocytoma	16
12	3rd ventricular tumor with obstructive hydrocephalus	62
13	3rd ventricular tumor with obstructive hydrocephalus	28
14	Subdural hematoma	10

TABLE 3

Congenital Hydrocephalus

Classification	No. Cases	GOT
		units
Internal	1	96
External	4	10–16

TABLE 4

Convulsive Disorders

	Type of Seizure	Ictal Stage	GOT
			units
1	Grand mal (status).	1–2 hr. post	30
2	Grand mal (status).	5 hr. post, 72 hr. post	40 20
3	Grand mal (status).	6 hr. post	14
4	Grand mal (status).	12 hr. post	12
5	Epilepsia partialis continua	during interval	38 10
6	Epilepsia partialis continua	during	34
7	Grand mal (status)*	during	100
8	Hemiballismus	during	20

* Patient died in status epilepticus.

TABLE 5

GOT of the Spinal Fluid before and after Electroshock Therapy

Name	Previous Treatments	GOT	
		Before ECT	After ECT
J. P.	7	30	38
C. A.	11	26	30
F. W.	2	18	24
J. M.	1	26	34

TABLE 6

Distribution of Transaminase Activity in Various Parts of Human Brain—Eight Hours Postmortem (Calculated at 37° C.)

	GOT μmole/hr./mg.
Motor cortex	0.68
Sensory cortex	0.64
Internal capsule	0.69
Cerebellum	0.83
Pons	0.78
Hypothalamus	0.52
Thalamus	0.54

vation of spinal fluid GOT activity, the size of the lesion and the clinical cause. In the present series of patients with cerebral vascular disease if one considers only those with GOT levels above the maximum normal values the following observations on prognosis can be made. Among 19 patients showing such an elevation, 13 died of the cerebrovascular accident or showed no neurologic improvement; 6 were improved. Patients whose GOT level was not elevated were 13 in number. Ten improved and 3 showed no improvement or died of their cerebrovascular accident. However, an attempt to gauge prognosis based on GOT levels is subject to possible error since there are certain cases in which at one time the GOT level is normal and yet on other occasions it is elevated. In the present series there were 23 patients from whom specimens were secured two or more times. Of these, 8 showed a normal value at one time, although at another time it was elevated. If one considers only those cases which exhibited elevated GOT activity on two or more occasions, then the prognosis appears much more reliable. There were 13 such cases, 10 of which resulted in no improve-

ment or death. The number of cases of acute cerebrovascular accidents presented here is probably not sufficiently large to apply statistical analysis. Nevertheless, there is a tendency for patients with elevated GOT levels to have a poor prognosis, while those with normal levels are more likely to improve.

Green *et al.* (5) mentioned several patients whose GOT level showed a progressive elevation. Two of these suffered from thrombosis of the internal carotid artery in which progressive cerebral deterioration is almost inevitable. In the present series one patient with internal carotid arterial thrombosis, as well as some of those with basilar arterial thrombosis, showed definite increasing levels of GOT activity. However, two patients with basilar arterial thrombosis showed normal levels of GOT in two examinations. The diagnosis of these two cases was confirmed pathologically; yet one patient with basilar arterial thrombosis (Case 15) with a typical history and physical findings showed a remarkable recovery with an elevation of GOT activity noted on two occasions. A third specimen from this patient taken approximately 2 weeks after the onset showed a return to normal levels. Because of the few pathologic specimens available, no statement can be made concerning the relationship between the GOT level and the size of the lesion. One patient with basilar arterial thrombosis (Case 10), whose GOT level was very high, showed extensive necrosis of large areas of both occipital lobes, the entire brain stem and both hemispheres of the cerebellum. Yet, two other patients with basilar arterial thrombosis whose GOT levels were normal showed infarction of the entire brain stem.

Brain tumors have been reported to show no elevation of spinal fluid GOT except for two cases reported by Fleisher *et al.* (4, 5). The present data are in agreement with these reports excepting cases in which obstructive hydrocephalus is present. From a consideration of this and other published series an elevated spinal fluid GOT would tend to indicate the absence of a tumor of the cerebral hemisphere.

Fleisher *et al.* (4) found elevation of GOT in 4 of 12 patients with a generalized convulsive disorder and 2 of 7 patients with focal seizures. Green *et al.* (5) noted elevation in 2 of 14 patients with convulsive disorders. Neither author mentioned the time when the specimens were taken in regard to the ictal manifestations. The present studies indicate that specimens taken only during or soon after a seizure show an elevation. Recent studies of temporal lobe lesions in convulsive patients have suggested that there may, indeed, be parenchymal damage from the repeated seizures. Although this might explain the GOT evelations, a more likely explanation would appear to be an alteration in cell membrane permeability. The absence of elevated GOT levels in hemiballismus suggests that the elevation of GOT in spinal fluids of seizure patients during or immediately after the seizures is unrelated to violent muscular activity.

SUMMARY

1. The control value of glutamic oxalacetic transaminase of the spinal fluid among 30 subjects was 16.8 ± 7.6 units.

2. A significant elevation of spinal fluid GOT in acute cerebrovascular accidents was noted in 9 out of 32 tested patients, comprising 28 per cent of the total.

3. In patients with acute cerebrovascular accidents high spinal fluid GOT levels tend to indicate poor prognosis and low GOT levels a favorable prognosis.

4. The spinal fluid GOT in patients with brain tumors was normal except in those with obstructive hydrocephalus. In one case of congenital internal hydrocephalus there was marked elevation.

5. The convulsive disorders showed elevated spinal fluid GOT only when the specimens were taken during or soon after the end of the convulsion.

6. The spinal fluid GOT was found to be

normal in the other neurologic diseases included in this series.

7. Transaminase levels in one human brain was highest in the cerebellum, followed by the pons, cerebral cortex and white matter, hypothalamus and thalamus, in that order.

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REFERENCES

1. Awapara, J. and Seale, B. Distribution of transaminase in rat organs. J. Biol. Chem., **194:** 497–502, 1952.
2. Braunstein, A. E. Transamination and the integrative functions of the dicarboxylic acids in nitrogen metabolism. Advances Protein Chem., **3:** 1–526, 1947.
3. Cohen, P. P. and Hekhuis, G. L. Rate of transamination in normal tissues. J. Biol. Chem., **140:** 711–724, 1941.
4. Fleisher, G. A., Wakim, K. G. and Goldstein, N. P. Glutamic oxalacetic transaminase and lactic dehydrogenase in serum and cerebrospinal fluid of patients with neurologic disorders. Proc. Staff Meet. Mayo Clin., **32:** 188–197, 1957.
5. Green, J. B., Oldewurtel, H. A., O'Doherty, D. S., Foster, F. M. and Sanchez-Longo, L. P. Cerebrospinal fluid glutamic oxalacetic transaminase activity in neurologic disease. Neurology, **7:** 313–322, 1957.
6. Karmen, A., Wroblewski, F. and LaDue, J. S. Transaminase activity in human blood. J. Clin. Invest., **34:** 126–133, 1955.
7. LaDue, J. S. and Wroblewski, F. The significance of the serum glutamic oxalacetic transaminase activity following acute myocardial infarction. Circulation, **11:** 871–877, 1955.
8. Magalini, S. I. and Stefanini, M. Studies on platelets. XVI. Glutamic oxalacetic transaminase activity of human platelets. Proc. Soc. Exper. Biol. & Med., **91:** 404–406, 1956.
9. Miyazaki, M. A note on determination of transaminase activity in bloody cerebrospinal fluid. Bull. School Med. Univ. Maryland, **42:** 61, 1957.
10. Miyazaki, M. Comparative serum and cerebrospinal fluid transaminase levels in acute cerebrovascular disorders. Bull. School Med. Univ. Maryland, **42:** 20–26, 1957.
11. Wakim, K. G. and Fleisher, G. A. The effect of experimental cerebral infarction on transaminase activity in serum, cerebrospinal fluid and infarcted tissue. Proc. Staff Meet. Mayo Clin., **31:** 391–399, 1956.
12. Wroblewski, F. and LaDue, J. S. Serum glutamic oxalacetic transaminase activity as an index of liver-cell injury from cancer. A preliminary report. Cancer, **8:** 1155–1163, 1955.

CLINICAL AND LABORATORY OBSERVATIONS ON LSD-25[1]

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Lysergic acid diethylamide was synthesized, in 1937, by Stoll and Hofmann (13–15). At present there seems to be agreement by most investigators on the clinically observed responses of human patients to the drug. The remaining questions seem to be, "How does it work?" and "What to do with it?" The first question implies an anatomic, biochemical and physiologic response. The second, almost anything from distorting spider webs and scaring salamanders to "shaking up" psychologic trainees or having LSD-25 social parties, to curing schizophrenia (2, 4, 5). *Ergo*, the research done is dependent upon the facilities available and/or the interests of the investigators. Our facilities, consisting of a 70 bed acute, intensive treatment section of a general medical and surgical Veterans Administration teaching hospital, lend themselves well to a twofold purpose: training residents and treating patients.

No animal laboratory is available to us. The only basic science help afforded our particular section is biochemistry, so that our laboratory work is necessarily limited to this field. We have attempted to utilize these facilities to answer in part the two questions posed.

Anxiety is accepted by most psychiatrists as being basic to all mental illnesses. The constellation of symptoms presented is thought of as the effort of the organism to defend itself against a threat. We do not mean to discuss the meaning of anxiety, or whether it is due to a twinge in the ascending reticular activating system or to castration fear, but rather are considering it as an accepted phenomenon and a useful construct. Moreover, we feel that the continuous repetition of any thought process is the form of all mental illnesses; that it is upon this we make the diagnosis of an illness. The content of the repetition gives us the type. Many authors have taken note of this process and have given it many names, such as circuitous firing circuits and positive feedback mechanisms, or (in a broad sense) Freud's "repetition compulsion neurosis." If one is to treat successfully a psychiatric illness this pattern must be disrupted. The analyst does this over a long period of time and occasionally finds himself repeating word for word a session that occurred a year previously with the same patient. Most important is the transference which he utilizes along with free association in an attempt to break up this obsessive thinking and activity, in order that the organism (ego) may go on to more constructive activity. Electroshock therapy, through the process of a thalamic and cortical discharge "blanks" the cortex; and we hope when cerebration returns that these pathologic thought processes will no longer be present. We have attempted (borrowing from both methods) to use LSD-25 as a therapeutic tool in the treatment of nonpsychotic patients. We may hypothesize that the modification of obsessiveness in reaction to LSD-25 occurs by way of an alteration of "reverberating circuits." This could be produced within the reticular activating system through a process of inhibition of the axodentric synapses with a concomitant facilitation of the axosomatic synapsis (11), thereby altering the external stimuli available to the cortex.

In our preliminary work with LSD-25,

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using physicians and psychology trainees as subjects, one of the first things noted, besides the obvious hallucinogenic qualities of the drug, was the rapid transference formed by the subject to the investigator. This transference was of a very strong nature and lasted throughout the test situation. Others have also written of this, notably Harold Abramson in his paper, LSD-25 Effect on Transference (1). Of special note was the fact that the transference gained was not dependent upon the experience or skill of the "therapist." This immediately opened the way to two methods of procedure, the most obvious being that of therapy with a patient. The second, that of teaching the handling and utilization of the transference process to residents and trainees. The latter may eventually prove to be more important than any therapeutic effect which may take place in the patient. Considering how best to use this transference, it was decided that Rosen's direct, interpretative technique would be the most efficacious and logical, since we were dealing with a psychotic process in which hallucinations, delusions, reality distortions, etc., were prominent. It was found that the patients readily accepted the interpretations and readily gained insight. Examples will be given in the case histories. Marked improvement was seen in psychoneurotic and nonpsychotic "obsessiveness" patients (nonstandardized nomenclature referring to chronic symptom complainers). An additional group of brain syndromes were treated but with no results.

An obvious objection to this method is that perhaps we have what is known as "transference cures." Aside from the fact that we accept readily any type of improvement or cure in the patient from whatever cause, Alexander has stated that he believes that some of his cures promulgated by two or three psychotherapeutic sessions were not of a "transference cure" nature but that the therapy formed a "wedge into the ego" as it were, and the ego was then able to go on and develop, thereby causing relief of symptoms in the same manner as any prolonged therapy might do. We hoped our therapy with LSD-25 would do just this, allow the ego to develop and expand, thereby forming the basis of a permanent change in the personality structure—or at the very least mitigate the crippling psychiatric condition.

A severe obsessive-compulsive patient was chosen (the extreme of obsessiveness) to demonstrate the ability of LSD-25 in breaking up circuitous thinking and activities. The description and results are given in Case 1. This case readily demonstrated our first hypothesis, and in so doing gave us an inkling of another type of therapy for the obsessive-compulsive patient, namely, "deconditioning." During the height of the reaction the patient was cajoled into doing things that ordinarily would cause an overwhelming amount of anxiety. This process was repeated over and over again. The most common response from the patient to this was, "I don't know how I can do this now. I don't understand this. I feel no anxiety at all and ordinarily it would frighten me a great deal." Following treatment it was found the patient could go on for days performing activities which were previously impossible for him. We hope to study more patients of this type, and to further our work along these lines. Few such patients are to be found in our institution.

METHOD OF TREATMENT

All patients were given complete physical and neurologic examinations, liver function tests, glucose tolerance tests and routine laboratory work The standard dose of 100 μg. of LSD-25 (Delysid), furnished by Sandoz Pharmaceutical Company, Hanover, New Jersey, in a fourth of a glass of distilled water was used uniformly. Treatment was given once weekly. If proper reaction did not occur the dose was doubled. On the morning of the treatment breakfast

was withheld. Each patient was placed in an individual room and assigned a primary therapist who stayed with the patient in periods ranging from 2 to 6 hours. No drug termination was made. The reaction was allowed to run its natural course. Control was accomplished using placebos. The same physician gave the drug at all times, and it was he who determined whether the drug or placebo(3) was being used. No one else was aware of whether the patient had water or LSD-25 until the reports were in at the end of the day.

A great latitude of freedom was afforded the therapist and the patient, *i.e.*, they ate together, smoked together and, if the patient wished he could get up and walk away from his therapist. Treatment was attempted in some 18 cases with a total of 52 treatments. The least number of treatments given was 1; the most for any one patient was 8. The total patient and treatment number does not include that carried out with the staff as subjects. Six cases are presented with their results. One should bear in mind that all of these patients had had extensive previous treatment with other methods without improvement. All had personality difficulties which would make improvement very unlikely, so that the staff considered any improvement a significant achievement.

Case Histories

Case 1. J. J. M., a 41 year old white, single, male veteran had classical symptoms of obsessive compulsive neurosis. He complained only of his inability to overcome his compulsive handwashing, of his avoidance of crowds for fear of "getting their germs," and of his compulsive doubting. He wore his trousers and sleeves rolled up, avoided shaking hands with anyone to avoid contamination and was first in the dining room and showers to be sure the food and water would not be "infected." His condition was of 14 years' duration and he had received a complete psychoanalysis, complete course of insulin and electroshock therapy and, of course, the gamut of drugs and various types of psychotherapy. He was placed on LSD-25 treatments, eight in number. His symptoms were treated at the height of the effect of the drug at each treatment; he was given direct interpretive psychotherapy and strong suggestion. Subsequently he shook hands without hesitation to bid farewell to other departing patients. He ate more regularly with concomitant gain in weight. His handwashing was definitely at a minimum. During additional LSD-25 treatments, direct psychotherapy was continued to break up his obsessiveness and "recondition" his patterns of thinking. His improvement at first was dramatic and sustained, but after termination of treatments he displayed recurrences, even though he was satisfied that, "At least I'm not as tense and anxious anymore." His improvement was minimal.

Case 2. M. E. E. W., a 35 year old Negro, married truck driver, complained of gastralgia, severe generalized cephalgia, general tenseness, vague myalgias and easy provocation to anger at work and at home; all since 1943. The symptoms were relieved, usually promptly, by taking an antiacid and walking away from or avoiding situations in which he felt irritable. At times, however, he acted out his anger and became involved in occasional fisticuffs. None of the complaints were typical in their course, frequency, location or severity. These behavior patterns never interfered with his sleep or vacations. There was no relationship to any specific marital, social or other interpersonal problem. Since 1943, he had entered several hospitals and always (including his current admission) his blood and serologic examinations, x-rays of the chest and skull, upper gastrointestinal series and electroencephalogram disclosed no pathologic conditions.

His past history included the presence of headaches most of his life. He was reared under strict, paternal discipline. He perpetuated a strong, passive-dependent relationship with his mother although there was conspicuous ambivalence toward her and subsequent female figures. His life theme throughout his adolescence and adult life was a striving for objects to gratify and sustain his state of dependency. Whenever his dependency was threatened, he showed sensitiveness, temper outbursts and at other times vascillated toward attitudinizing, aloofness and withholding his anger. In school

he managed to progress to about the eighth grade despite truancy and disinterest in his studies. In interpersonal associations he had little ability to give or sustain affection and exploited relationships chiefly for narcissistic gains. Occupationally, he displayed emotional instability resulting in frequent job changes.

In the hospital he was inclined to demonstrate a parasitic social existence. At times he was charming and confidence-inspiring, then at other times, surly, complaining and resentful. He frequently complained of his symptoms which were seldom consistent. He never remarked on relief despite participation in psychotherapy, tranquilizing medication and the ancillary therapies.

During the LSD-25 treatments the patient had an intensification of his somatic symptoms. At the peak of effect of the drug he became wide eyed with undescribable fear. He re-experienced strained interpersonal situations during which he recalled arguing with authority figures. He reported he was in communication with Jesus Christ and, as he states, "I felt like I was walking in the shadow of the valley of death and, like Him, was being born all over again." At this point he was given the interpretation that he had repressed considerable hostility toward his father and basically had always felt the absence of a healthy identification with him or other substitute figures; this defect in psychosexual development was presented along with his passive-dependent relationship with his mother which the patient accepted with further rememberances of situations to confirm this After four such treatments he requested to leave the hospital to attempt an extramural adjustment in a productive role once more. He has sustained improvement to this date.

Case 3. J. B. K., a 26 year old Greek-American man, married two years, began to notice the onset of headaches, chest pains, fluttering of the heart, and generalized weakness about the time of the birth of his first child. His longitudinal development revealed early childhood restrictions under a patriarchal atmosphere with a compromising, indulgent mother. A strict moral code and social obedience fostered suppression of heterosexual relationships along with feelings of indecisiveness and marginal self-confidence. His family had always been financially secure and provided the patient with employment in their restaurant. This dependency state was further intensified by frequent childhood illnesses such as allergies and an above average number of mild ailments. He could never assert himself within the family circle or among his peers. By repression and suppression, and the assumption of passive, conforming behavior, the patient was reasonably successful in controlling his hostility. His marriage was an attempt to emancipate himself from this infantilized role. He was assured continued employment with his family's support and he could not turn his back on his parents' "helpful" advice.

The patient was involved in a minor truck accident during which he suffered mild muscle injuries to the back. This apparently had considerable meaning to him as he repeatedly referred to it as the etiology of his current difficulties.

Prior to the birth of their first child he realized that overwhelming and anxiety-provoking responsibilities were forthcoming. His anxiety was bound by somatization and affective channeling through the autonomic system, in the form of the initial symptoms. He responded to none of the psychotherapeutic or other ancillary therapies or to ataractic medication. His complaints were frequent and irregular throughout the day and night. They varied at times and "never were quite gone . . ."

Under LSD-25, he relived the experience of the truck accident and developed a paraplegia in extension which was quickly relieved by direct interpretation of his wish to remain completely helpless and dependent. He also abreacted emotional tension and apprehension which he had experienced and which had been repressed since the accident. He received three LSD-25 treatments and his progress has been stable.

Case 4. E. P. is a 26 year old, unmarried, Mexican-American male veteran with a 10 year history of atypical symptoms of headache, nausea, myalgias, gingival discomfort, temper outbursts and vague tinnitus. The personality development was passive-dependent. Identification was with an emotionally demonstrative, weak mother. He avoided heterosexual relationships except with prostitutes. School and work adjustment were unstable and characteristically

acceptable only with those who granted him favors and condoned his mediocre talents. He had several hospitalizations and had received various types of psychotherapy and various medications.

Under LSD-25 treatments the patient experienced a visitation of the Virgin Mary standing on a pedestal which was interpreted as symbolic of the purity he saw in women, especially his mother. The relationship between this and his evasions of marriage or of mature love was pointed out. His improvement has also sustained itself to this date.

Case 5. R. M. M., a 34 year old Mexican man, married, with five children, complained of intractable aerophagia, chest pain, gastralgia and flatus over a period of several years. His longitudinal history indicated tumultuous family influences with rejecting and depriving parents and much sibling rivalry. His school and work histories were likewise poor and under any increased stress in ordinary interpersonal relationships his frustration could only be quelled with the use of alcoholic beverages. He received much psychotherapy, hospitalization, specially arranged ancillary therapy and carefully planned and scheduled medical regimen. Laboratory reports were negative. No improvement was ever admitted by the patient or discerned by the staff.

Under LSD-25 treatment the patient reported living again as an infant. The interpretation was made that he was "still sucking on the bottle, just as an infant, and that in this state he need not be concerned about his expected obligations to his family, etc." During the subsequent treatments, he slowly accepted the meaning of his infantilized behavior and need to be nursed and cared for. The aerophagic symptom disappeared although his chest pain persisted. His response was considered good. Then he developed a depression characterized by crying spells and thoughts of suicide. He received a course of electroshock therapy and reported a remission of his chest pain along with the depression. He was improved enough to be discharged.

Case 6. E. S. N., a 43 year old white, married man, retired from the Marine Corps, complained of severe, cervical muscle spasm of about 1½ years' duration. His laboratory and x-ray reports were all normal. He did not respond to psychotherapy, hypnotherapy or tranquilizing drugs. His past history was without definite emotional disturbances from the patient's point of view. He was exposed to a strict Roman Catholic family milieu. He extricated himself from a yoke of religious limits by enlisting in the U. S. Marine Corps and dissociating himself from Catholicism.

Under the LSD-25 treatments the patient experienced an intensification of his muscular tension and reported visual hallucinations. These were described as follows: "I saw my wife and children standing next to my mother's grave . . . just to one side God was also present; I felt as though I were a spectator to a scene full of meaning to me." He remarked that he felt as though he was "crying on the inside" all during this time. It was interesting that this patient was repeatedly urinating at intervals during the treatment. He unhesitatingly accepted the interpretations that this "scene" evoked repressed guilt feelings; as he exclaimed, "This is the way I've felt ever since I lost my faith; I let my mother and God down. . ." Following three such treatments the patient was no longer troubled with insomnia and felt markedly tranquil, although his muscle spasm was not entirely relieved. The degree of improvement was also fair, to the point of his preparing for release from the hospital and a return to his religion.

LABORATORY DATA

Most of the individuals receiving LSD-25 were sampled for circulating eosinophils before, and 1 and 4 hours after the ingestion of the drug. Eosinophil counts were obtained using the Randolph technique (12). Fifteen subjects were tested; 10 of them received 0.1 mg. LSD-25 orally, 2 to 6 times at weekly intervals. Control days with no placebo or medicant, placebo days and stimulant controls with adrenaline and/or ACTH were run.

All normal individuals and all patients but one responded with a decrease (40 per cent or more) in eosinophils following the ingestion of 0.1 mg. of LSD-25. The one patient who failed to respond to 0.1 mg. subsequently lost 75 per cent eosinophils

after 0.2 mg. LSD-25. A block or tolerance to the medicant was observed upon repeated weekly doses. This occurred in one patient on his third course of LSD-25. At this time he also failed to respond to 0.3 ml., 1 to 1000 adrenaline, s.q., but did produce an eosinopenia with 25 units of ACTH, i.m. Prior to this block he had developed decrease in eosinophils following adrenaline. A second patient also failed to show a response on the second course of the medicant. The first 0.1 mg. resulted in a decrease in eosinophils followed by a failure to respond to adrenaline. The next weekly LSD-25 treatment failed to produce a significant decrease as did adrenaline and ACTH. The following week satisfactory decreases were obtained with 0.2 mg. of LSD-25 and 40 units of ACTH but he still did not react to 0.6 ml. of adrenaline. A third patient developed an eosinopenic response to LSD-25 but did not react to the standard dose of adrenaline.

Chronic use of reserpine has previously been shown (7) to be able to block the eosinopenia normally produced by adrenaline.

All placebo procedures failed to produce an eosinopenia even in a patient who subjectively reported a "terrific reaction," "Strongest dose I've had yet." The primary therapist however reported no response in agreement with the physiologic observation.

DISCUSSION

LSD-25 (0.1 mg. orally) initiates a series of events of which one, a physiologic response, is a decrease in circulating eosinophils. It has been shown by Porter (10) that the eosinopenic response in cats can be evoked by stimulation of the tuberal or mammillary areas of the central nervous system and can be blocked by an electric lesion in the posterior hypothalamus. The mechanism of the eosinopenia can be initiated by adrenaline or a nonspecific stress acting in the hypothalamic area. This stimulates the pituitary to release ACTH activating the release of adrenal corticoids that results in the decrease in eosinophils. The development of a block in this response by LSD-25 that also blocked the response to adrenaline but not to ACTH suggests that the pathway for this action of LSD-25 may be the same or similar to that of adrenaline.

The two examples of an eosinopenic response to LSD-25 with failure to react to adrenaline may demonstrate a differential sensitivity to the two stimulating agents. There is also the possibility that the adrenaline is inactivated or that its stimulus is blocked prior to the point at which LSD-25 is effective.

Recent animal work of K. Killam (8) implicates the thalamus in the central nervous system's response to LSD-25. These data were obtained by electrode placement in unanesthetized curarized cats.

Further data focusing on the central nervous system have been reported by Olds, Killam and Eiduson (9). Their test preparation is the implanted electrode in rats and the measure of response is a press bar rate. This system gives reproducible results and allows for accurate electrode placement. Their results indicate that the primary response of LSD-25 is a general decrease in press bar rate. The response in the olfactory tubercule of the forebrain and tuber cinereum of the hypothalamus region can be completely blocked with serotonin while the stimulus in lateral placements was not antagonized. Brom LSD-25 was only effective in areas where serotonin blocked LSD-25.

One is tempted to relate the LSD-25 symptomatology, the eosinopenia and its blockade in man to this animal work and to the cortical projection system from the midbrain, subthalamus and hypothalamus of French *et al.* (6). This projection system also involves the cortical sensory responses of sound and sight which also strongly respond to LSD-25.

All of the following responses of LSD-25

can be directly or indirectiy related to the hypothalamus-thalamus area of the central nervous system. The constellation of clinical symptoms primarily centered around the hallucinations with the senses of sight and sound having a significant part. The production of an eosinopenia, its affiliation with adrenaline and the blockade of LSD-25 on both stimuli as it was demonstrated in man, the observations by electrode placement in both cats and rats all point to this region as the site of LSD-25 action in the central nervous system.

For what it may be worth, we have had two cases of "hypothalamic syndrome" both of which were preceded by symptomatology similar to that seen during an LSD-25 intoxication. In one case the hallucinatory phenomena appeared 5 days before the other symptoms. These consisted of temperature of over 109° C., status epilepticus and hematemesis. All symptomatology, including the hallucinations, completely cleared within 24 hours. As an incidental result there has been a complete personality change in the patient for the better.

The second case was a paraplegic who, immediately after his accident, had hallucinations, diabetes insipidus and loss of temperature control. All three cleared simultaneously. One could postulate that the focus of irritation was acting at the same level as did the LSD-25.

CONCLUSIONS

1. LSD-25 can be used to demonstrate the integration of basic neurophysiology with well known concepts of psychopathology.

2. LSD-25 has the astonishing quality of bringing into focus the patient's repressed emotional attitudes, conflicts, etc., and permits their reactivation. The hallucinatory experiences are not always symbolic, but in the majority of the patients these were not difficult to interpret with knowledge of the patient's developmental history, defenses, etc.

3. The intense transference develops and may be capitalized on with direct, interpretive, Rosen type psychotherapy centering on the reexperiences as well as for reconditioning or "breaking up" of obsessiveness circuits in favor of more appropriate thinking circuits. Improvement was also produced by psychocatharsis.

4. LSD-25 effects are mediated through the reticular activating substance and hypothalamic-pituitary-adrenal axis, as demonstrated physiologically.

5. In the number of cases presented, most had placebos for control and all except the chronic brain syndromes demonstrated some degree of improvement in the sense that they were able to return to society and their families in a more productive capacity.

REFERENCES

1. Abramson, H. A. Lysergic acid diethylamide (LSD-25). XIX. As an adjunct to brief psychotherapy with special reference to ego enhancement. J. Psychol., **41:** 199, 1956.
2. Abramson, H. A. and Evans, L. T. Lysergic acid diethylamide (LSD-25). II. Psychobiological effects on the Siamese fighting fish. Science, **120:** 990, 1954.
3. Abramson, H. A., Jarvik, M. E., Levine, A., Kaufman, and Hirsch, M. W. Lysergic acid diethylamide (LSD-25). XV. The effects produced by substitution of a tap water placebo. J. Psychol., **40:** 367, 1955.
4. DeShon, H. J., Rinkel, M. and Solomon, H. C. Mental changes experimentally produced by LSD (D-lysergic acid diethylamide tartrate). Psychiatric Quart., **26:** 33, 1952.
5. Forrer, R. and Goldner, R. D. Experimental physiological studies with lysergic acid diethylamide (LSD-25). Arch. Neurol. & Psychiat., May, 1951.
6. French, J. D., Von Amerongen, F. W. and Magoun, H. W. An activating system in brain stem of monkey. Arch. Neurol. & Psychiat., **68:** 557–590, 1952.
7. Goodman, J. R., Florsheim, W. H. and Tempereau, C. E. Reserpine and thyroid function. Proc. Soc. Exper. Biol. & Med., **90:** 196–198, 1955.
8. Killam, K. F. Studies of LSD and chlorpromazine. Psychiat. Res. Rep. No. 6, Am. Psych. Assoc., Oct., 1956.

9. Olds, J., Killam, K. F. and Eiduson, S. Effect of tranquilizers on self-stimulation of the brain. International Symposium on Psychotrophic Drugs, Milan, Italy, May, 1957. (To be published by Springer, Vienna.)
10. Porter, R. W. Hypothalamic involvement in the pituitary-adrenocortical response to stress stimuli. Am. J. Physiol., **172:** 515–519, 1953.
11. Purpura, D. P. Electrophysiological analysis of psychotogenic drug action. II. General nature of lysergic acid diethylamide (LSD) action on central synapses. Arch. Neurol. & Psychiat., **75:** 132, 1956.
12. Randolph, T. G. Differentiation and enumeration of eosinophils in the counting chamber with aglycol stain. J. Lab. & Clin. Med., **34:** 1696, 1949.
13. Stoll, A. and Hofmann, A. Partial synthesis of alkaloids of the ergometrine type, Helvet. chim. acta, **26:** 944, 1943.
14. Stoll, W. A. A new hallucinatory agent, active in very small amounts. (Proceedings of the 108th meeting of the Swiss Society of Psychiatry, November, 1947, Zurich) Schweiz. Arch. Neurol. u. Psychiat., **64:** 483, 1949.
15. Stoll, W. A. LSD, a hallucinatory agent from the ergot group. Schweiz. Arch. Neurol. u. Psychiat., **66:** 1947.

SOME PHARMACOLOGIC CORRELATIONS OF THE CHEMOTHERAPY OF MENTAL DISEASE

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The rapid application of the tranquilizing and central nervous system (CNS) stimulating drugs to the treatment of mental disease and other nonpsychopathologic disorders of the mind has far surpassed the rate of development of an experimental basis for their mechanism of actions. Thus, there exists a greater knowledge of the effects of these drugs on the human organism than of the specific alterations of the nervous system which produce these actions. The extensive use of these drugs and their unusual nature have stimulated many investigations into their basic pharmacologic mechanisms which have now begun to close this gap in our knowledge. However, many areas of missing information and contradiction still exist.

These deficiencies are attributable mainly to the extreme complexity of cerebral functions and to the lack of sensitive, specific and simple methods with which to study the problem. The advent of the tranquilizing drugs, in 1954, found only a few biochemical and neurophysiologic techniques applicable to the study of drug action on the brain. Quantitative methods for the measurement of behavioral activity as affected by drugs were particularly meager. These drugs have stimulated great strides in the development of suitable methodology. Biochemical analysis of the constituents of localized brain areas and the enzymatic study of the particulate components of neural tissues have been adapted to drug investigation. Improved techniques of EEG analysis such as the use of implanted depth electrodes and the study of evoked neuronal potentials have been most beneficial. Finally a whole new field of behavioral analysis has developed many statistically reliable methods which have measured more sensitive effects of these drugs than were possible with pharmacologic techniques.

The greatest problem confronting one attempting to correlate the clinical action of drugs in mental illness with laboratory data is the lack of general acceptance of any single hypothesis for the pathogenesis of these diseases. Indeed, even the diagnostic classification of disorders such as the schizophrenic reaction is subject to debate. Coupled with this is the highly subjective nature of most measurements of clinical improvement in the patient's condition. Such achievements by the patient of "social recovery," "good ward adjustment," "verbalization of problems" and "insight" are poorly amenable to quantitative interpretation. The extremely labile response of psychiatric patients to placebo therapy is well known (55, 168). In a recent study merely the transfer to another ward for research study resulted in measurable improvement in 39 of 48 patients (228).

This survey of recent investigations of the tranquilizing (or ataractic) and the CNS stimulating drugs which have been applied to the treatment of mental disorders will attempt, where possible, to correlate and explain the observed clinical actions of these drugs with laboratory demonstrated mechanisms and to assemble some tentative hypotheses for their mode of action.

DEPRESSIVE REACTIONS

Although electric shock therapy (EST) remains, at present, the foremost form of somatic treatment for the various forms of mental depression (with the possible excep-

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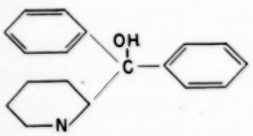
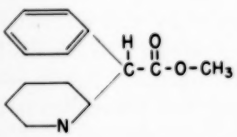
tion of the manic-depressive form of the schizophrenic reaction) many new forms of CNS stimulating and convulsing drugs continue to appear and be tested for this type of mental disease. This reflects a basic dissatisfaction on the part of both the psychiatrists and patients for this effective, yet distasteful form of therapy.

CNS Stimulating Drugs. Compounds such as dextroamphetamine (Dexedrine) and methamphetamine (Desoxyn, Norodin, Pervitin, Drinalfa, Methylisomyn, Methedrine, Isophen, Syndrox, Dexoval, Efroxine and Amphedroxyn) have been used as daytime emotional stimulants (162) and as aids to psychotherapy (179, 268, 273). It is difficult to control doses and dosage schedules in order to avoid insomnia and to achieve therapeutic success.

Two more recent drugs with CNS stimulating properties, but lacking the peripheral autonomic effects of the above sympathomimetic agents are pipradrol (Meratran, Merrell) and methylphenidylate (Ritalin, Ciba). Both of these compounds are piperidine derivatives as shown in the accompanying formulas. The ability of these compounds



PIPRADROL
(MERATRAN)



METHYLPHENIDYLATE
(RITALIN)

to cause increases in the spontaneous coordinated activity of animals without evidence of sympathomimetic side effects such as tachycardia, rises in blood pressure, etc. (44, 201) has led to their use to combat fatigue, lethargy and other depressive moods (18, 65, 80, 89, 139, 184, 250). Although some clinicians have reported successful therapy of reactive and involutional depression with pipradrol, others have been in disagreement with this claim (2, 95, 241).

Pharmacologically, both of these compounds should be classified as subcortical, rather than cortical stimulants. Rinaldi and Himwich (237) suggested from EEG effects that pipradrol acted by stimulating the reticular activating system of the mesodiencephalon. Methylphenidylate also has an arousal effect on the EEG as evidenced by a shortening of the barbiturate sleep pattern when both drugs are given intravenously (190). The drug also has an antihypertensive action (199).

The introduction of iproniazid (Marsilid, Hoffman-La Roche) into the treatment of mental depressions (247) represents a different approach to the production of CNS stimulation. It is likely that iproniazid, through its inhibition of monoamine oxidase in the brain, potentiates the action there of endogenous stimulant substances, possibly norepinephrine, epinephrine, and serotonin (5-hydroxytryptamine). Thus it produces a more natural stimulation as compared to the use of exogenous sympathomimetics. Another apparent advantage of iproniazid over conventional sympathomimetic therapy is the more gradual onset and the less fluctuating nature of the stimulation. The administration of 50 up to 150 mg. per day gives an effect within 1 to 2 weeks. Excessive dosage may lead to an acute psychosis, which is, however, reversible. Most of the side effects (constipation, difficulty in micturition, hyperreflexia, sweating, dryness of the mouth), with the possible exception of dizziness and postural hypotension, are compatible with a hypothesis of peripheral sympathetic stimulation. Iproniazid has been recommended both for mild depressions and for the psychoses associated with severe depression or regression as well as other nonpsychiatric uses. It should not

be used in hyperactive, agitated patients, or in those with impaired kidney function or epilepsy. Coadministering the drug with ether anesthesia, meperidine or another amine oxidase inhibitor such as cocaine should be avoided. There is an added hazard that the simplicity of oral therapy with nonconvulsant forms of therapy may result in abuse through lack of close supervision and psychotherapy essential for complete cure.

CNS Convulsant Drugs. At least four recent innovations have appeared in the field of pharmacoconvulsive therapy in attempts to eliminate the basic disadvantages of EST and pentylenetetrazole (Metrazol, Cardiazol) in the induction of convulsive treatment for mental depressions. All are still in the stage of controlled clinical study, but seem worthy of further examination. Besides the factor of rejection by the patient, EST has the other disadvantages of postictal apnea, confusion and amnesia. Cardiac complications exist and the liability to fractures has been overcome only at the added risk imposed by the use of muscle relaxant drugs. Pentylenetetrazole has fallen into disuse largely because of the difficulties of regulation of intravenous doses and the feeling of overwhelming anxiety which precedes the convulsion.

Indoklon (hexafluorodiethyl ether) introduced by Krantz *et al.* (163, 163-A) is a volatile, nonflammable, pleasant smelling liquid with a boiling point of 64° C. It is capable of the rapid induction of a full grand mal type seizure, preceded by unconsciousness, upon less than 20 seconds' inhalation of concentrations as low as 30 p.p.m. in the inspired air. Even so, the convulsion induced is more gradual in onset than for EST. The apnea accompanying the tonic phase of the full cortical seizure affords a self-regulating mechanism for determining the minimal effective dose. This overcomes the former disadvantage of pentylenetetrazole over- or underdose. Postictal apnea, confusion and amnesia have been noticeably less than for EST in more than 40 patients (78, 164). The rapidity of action of this convulsant suggests an action on the neural membrane. Pharmacologic experiments have rejected hypoglycemia, anoxemia and anticholinesterase activity as possible mechanisms. The onset of the EEG pattern of cortical dysrhythmia produced by Indoklon in the animal treated with muscle relaxants resembles the spike and slow wave pattern of pentylenetetrazole and the myoclonic type of petit mal epilepsy before the multiple spiking of the full cortical seizure occurs.

A second new pharmacoconvulsive agent is also chemically derived from an unexpected source. The compound P.M. 1090 (2,2,3,3-tetramethylsuccinamide) bears a resemblance to drugs with anticonvulsant activity, but produces convulsive seizures when given orally or intravenously. Nausea, vomiting occasionally, and additional convulsions are problems in this type of therapy (72).

A method of reducing the convulsant threshold of pentylenetetrazole has been the use of flickering light (14 to 20 per second) with lower doses of the convulsant (108). More recently, hexazole (Fazole, Azozol, Azoman, Triazole), a related compound, has been similarly applied (283). Pfeiffer *et al.* (218) have described the use of some semicarbazides which produce a convulsion, likely through the mechanism of a cerebral pyridoxine deficiency. The compound thiocarbohydrazide ($H_2N—NH—C(:S)—NH—NH_2$) given in an oral dose of 200 mg. was found to induce a grand mal seizure 1 to 2 hours later in the patient who remained lightly restrained in his own bed. The convulsion is aborted by the intravenous injection of 50 to 200 mg. of pyridoxine. The undesirable side effects noted were nausea and occasional production of a temporary state of epilepsy.

None of these foregoing innovations has shown as yet a clinical superiority in successful results much greater than those

achieved by EST. However, they do represent attempts at improvement and increased patient acceptance of stimulant therapy.

THE SCHIZOPHRENIC REACTION

In contrast to depressive reactions, pharmacotherapy with the tranquilizing (ataractic) drugs, since 1954, has largely replaced electric shock therapy as the principal form of treatment for most forms of the schizophrenic reaction. Although the relative value of the therapeutic effect of these drugs may be inversely proportional to the quality of treatment supplied to the patient before their introduction, it is generally conceded that these drugs have a useful function in the control of the acute psychosis and in some of the chronic phases of this disease.

The question of what defines a tranquilizing drug and which of the many drugs which are called tranquilizers may qualify under that definition is undecided by any consensus of opinion. This confusion arises by reason of restriction of the term "tranquilizing drug" by some persons to those drugs which are capable of calming the overt reactions associated with acute schizophrenic psychoses, whereas others extend the term to embrace all drugs useful as psychosedative agents. Perhaps for the former restriction the terms "psychototherapeutic" or "antischizophrenic" would be better. For the restricted area a tranquilizing drug may be defined as one that normalizes certain hyperemotional conditions such as mania, hallucinations and extreme anxiety and tension states without producing concomitant CNS depression such as drowsiness, confusion and motor incoordination. Barsa has pointed out that some tranquilizers may affect the hallucinations, delusions and psychotic behavior more specifically than they produce relaxation of anxiety and tension (15). According to this definition only certain of the more potent phenothiazine derivatives, certain *Rauwolfia serpentina* alkaloids and perhaps meprobamate would qualify as being truly antischizophrenic drugs. Although meprobamate has shown effectiveness in some studies with acute and chronic psychotics (37, 215, 253, 254, 281), its discussion is best deferred to the section on treatment of the psychoneuroses, for which it has been more widely used.

The drugs most widely in use in the United States for the treatment of the schizophrenic reactions are shown in Table 1.

Many other compounds exist in addition to those listed (especially in the phenothiazine category). Some of these have had limited clinical trial such as ethylone-3-dimethylamino-3′-propyl-10-phenothiazine (acetylpromazine, CB–1522) (67, 140) and piperidinochlorphenothiazine (NP–207, Sandoz) (113, 153, 187). Other drugs such as atropine in large doses have been recommended for the treatment of schizophrenia (94). It has been noted that the schizophrenic responds with a lucid interval to stimulation by cholinergic drugs such as pilocarpine, arecoline and more recently the chronic administration of 2-dimethylaminoethanol (219). Undoubtedly other drugs will appear until the rational basis of drug therapy in this condition is more apparent.

For review purposes it may be assumed that reserpine and chlorpromazine are prototype drugs and are qualitatively representative of their respective groups. Quantitative differences exist, especially among the phenothiazine derivatives. In fact, there are clinical findings suggestive that some of the phenothiazines such as chlorpromazine are principally adrenergic blocking in side actions whereas others such as mepazine exert cholinergic blocking actions as their main side effects (38). Whether these two drugs differ also in the mechanism of their tranquilizing action is, however, not yet apparent. Differences between reserpine and the action of the total alkaloids of *Rauwolfia* on the sleep centers have also been found (102).

Many comparative studies have been

TABLE 1

Commonly Used Drugs in the Treatment of Schizophrenic Reactions

Generic Name	Proprietary Names	Pharmaceutical Firm
Rauwolfia serpentina alkaloids		
Reserpine	Serpasil	Ciba
	Sandril	Lilly
	Reserpoid	Upjohn
	Serpiloid	Riker
	Serfin	Parke-Davis
Rescinnamine	Moderil	Pfizer
Deserpidine (canescine, recanescine, raunormine)	Harmonyl	Abbott
Phenothiazine derivatives		
Chlorpromazine	Thorazine	Smith, Kline & French
Promethazine	Phenergan	Wyeth
Promazine	Sparine	Wyeth
Mepazine	Pacatal	Warner-Chilcott
Prochlorperazine	Compazine	Smith, Kline & French
Perphenazine	Trilafon	Schering
Triflupromazine	Vesprin	Squibb
Diphenylmethane derivative		
Azacyclonol	Frenquel	Merrell

made between reserpine and chlorpromazine for the treatment of the hospitalized schizophrenic. Several reviewers have pointed to chlorpromazine as generally the more valuable drug (11, 167, 191), while one has found no significant differences in his own experience and in his analysis of the literature (99).

Rauwolfia serpentina Alkaloids

Reserpine. The pharmacology of *Rauwolfia serpentina* has been reviewed (19). The applications of the principal alkaloid, reserpine, to hypertension (3) and to neuropsychiatric uses (4) have been the subject of extensive discussions. From these have emerged the cardinal features of the reserpine induced syndrome. Its central sedative action, unlike that for other CNS depressants, is characterized by a state of imperturbability with a tendency toward drowsiness, but without depression of contact with environmental stimuli and without a loss of coordination in responses to these stimuli. However, hyperemotional responses mediated by sympathetic centers in the hypothalamus are markedly depressed.

Peripherally, the syndrome is marked by bradycardia and slight lowering of blood pressure, stimulation of peristalsis leading to increased frequency of stools, gastric hypersecretion, miosis, ptosis of the eyelids and, in animals, a relaxation of the nictitating membrane. Larger doses may inhibit the respiratory and temperature regulating centers although this is seldom encountered with clinical dosage.

Centrally, such a pattern of signs and symptoms resembles that generated by several conditions. One of these is that in patients with tumors of the posterior hypothalamus (sympathetic areas) (103). This led Schneider *et al.* (248) to suggest that reserpine exerted a blocking action against afferent stimuli to this emotional center. However, the site of the blockade was not defined.

Other neurophysiologic studies have recently given attention to certain rhinencephalic centers as possibly being involved in the emotional instability of the schizophrenic. These have reactivated interest in the original theory of Papez (213) that these centers in the "nose" brain may have emotional as well as olfactory function (183, 227). Many similarities have been noted between reserpine produced sedation and the effects of neural damage or removal in mon-

keys of certain of these areas such as the amygdaloid complex, portions of the temporal lobes and the prepyriform cortex (157, 288). The presence of these areas has been shown to be necessary in order for reserpine to have a depressant effect on conditioned avoidance of electric shocks by monkeys (272). Chronic reserpine administration has produced an enhancement of rhinencephalic seizure activity as recorded from electrodes implanted in the amygdaloid and hippocampal regions in unanesthetized cats (151, 267).

These observations, however, are difficult to correlate with observations of amygdaloid seizure activity in conjunction with excited behavior in cats (177) and slow wave activity of high amplitude from electrodes placed in the amygdala and hippocampus in humans in conjunction with recall of turbulent emotional experiences and odors associated with those experiences (176, 204). A close relationship has been observed between patients with certain forms of psychomotor epilepsy and psychotic symptoms similar to those of the schizophrenic when the EEG shows disturbances in the temporal and underlying lobes (240).

Two possible explanations of how reserpine might act at these rhinencephalic sites include: (*a*) stimulation of inhibitive mechanisms controlling the hypothalamic emotional centers (248), or (*b*) the causing of an increase in cortical inhibitive pathways (284). Other explanations revolve about a reversal of activity of reserpine according to the dose used (19). Although it appears that the amygdaloid complex is important as a coordinator of behavioral activity (260) more precise studies of functional localization will be necessary in order to explain drug action in this part of the brain.

A second area of neurophysiologic research has been the action of reserpine on the ascending reticular activating system (207) and the diffuse thalamic projection system (147, 206). These two systems are sometimes referred to jointly as the mesodiencephalic activating system, since the diffuse thalamic projection system may be partially the afferent pathway to the cortex of stimuli from the reticular area (131). Recently two components have been distinguished within the reticular activating system (69, 70, 242). One component having cholinergic synapses is activated by diisopropyl fluorophosphate (DFP) and physostigmine and blocked by atropine. An adrenergic component located more caudally is activated by epinephrine, norepinephrine and amphetamine and blocked by chlorpromazine. The activation of the former results in EEG desynchronization (fast activity) only, while adrenergic stimuli provoke both similar EEG changes and behavioral arousal effects.

The effects of reserpine on the scalp EEG are slight and variable (19, 284). In contrast to the barbiturate sedatives it does not produce the slow wave activity and synchronization characteristic of sleep patterns. Prolonged therapy may produce alterations to a fast activity pattern (22, 194).

Small doses of reserpine have little effect on the EEG activation or the behavioral arousal in anesthetized cats following stimulation in the reticular formation or stimuli placed in the nuclei of the diffuse thalamic projection system (151). However, large doses in rabbits potentiated and prolonged arousal stimuli in the mesodiencephalic activating system (236). Although these effects of large doses on the EEG and its activation do not seem directly related to the tranquilizing activity of reserpine, they are likely the explanation of the Parkinson-like tremor which occurs in patients after extended therapy. They may explain the facilitating action of the drug on drug induced convulsions by caffeine and pentylenetetrazole and its lowering action on the electroshock threshold (52). It may also explain some of the disastrous results reported from the application of EST to some reserpinized patients, although the combination has been given to hundreds of other individuals with-

out adverse reactions (191). Still, no significant change in the schizophrenic human threshold to convulsions with hexazole was found after repeated large doses of reserpine (40).

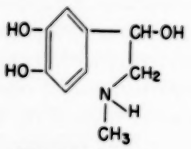
Experimental measurements of the sensitivity of hypothalamic and medullary centers have shown that these are not depressed by reserpine. This has suggested that the site of action of reserpine is on the afferent pathways to these centers (121, 249). Other investigators (30, 138) have presented evidence of depression of medullary centers by reserpine. This contradiction has been attributed by Bein (19) to differences in the dose of reserpine.

Biochemical and pharmacologic evidence on the mechanism of reserpine action has been far less localized than neurophysiologic data, but has been quite revealing as to the nature of the fundamental cellular action. This mass of data has been accumulated largely as a result of the very speculative hypotheses of Woolley and Shaw (294) and Gaddum (104). These were based on the finding of serotonin (5-hydroxytryptamine) in the brain and the knowledge that peripherally serotonin antagonized the action of the hallucinogenic drug lysergic acid diethylamide (LSD) on the intestine. These hypotheses were expanded later, largely through the work of Brodie's group at the Laboratory of Chemical Pharmacology at the National Heart Institute, into a theory of reserpine action based on its liberation of serotonin from a bound form in brain tissues and through the action of this substance on the brain (43, 222, 261, 262, 265). The theory was also extended to a concept that serotonin and norepinephrine were neurochemical transmitters with opposite types of actions in the synapses of the autonomic centers of the lower brain. They also proposed that the differences in action between chlorpromazine and reserpine could be explained on the basis that the former is an inhibitor of norepinephrine and the latter a stimulator of serotonin release (42).

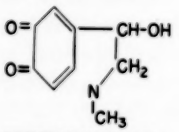
Attractive though this theory may be it has been subject to enough criticisms (19, 31, 33, 51), as well as support (63, 295) to make it worthy of reexamination. This is especially pertinent in view of recent evidence demonstrating reserpine to cause release of brain norepinephrine in a very parallel fashion to its action on serotonin (47, 50, 135, 264, 277).

Before commencing such an analysis it may be useful to point out many other preexisting evidences of a close association of serotonin with the sympathetic division of the autonomic nervous system.

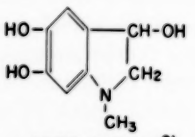
(1) Chemical similarity between the indole structure of serotonin and some of the postulated metabolites of epinephrine.



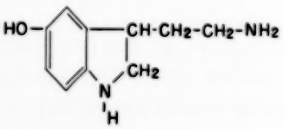
EPINEPHRINE



ADRENOCHROME



ADRENOLUTIN[91]



SEROTONIN

(2) Biochemical similarity in metabolism by monoamine oxidase (32, 100, 115, 269) and in the distribution of this enzyme (34, 35). Although epinephrine and norepinephrine are also substrates for this enzyme (263), doubt has been expressed that mono-

amine oxidase is important in adrenergic metabolism (117, 158).

(3) Pharmacologic evidence of an epinephrine-like inhibition of cerebral synaptic transmission (192, 193), a similar cardioaccelerator function to epinephrine in invertebrate hearts (93, 290) and a somewhat similar pattern of antagonism by adrenergic blocking agents (76, 105). Recently serotonin has been isolated from perfusates of sympathetic ganglia (111).

The Brodie theory of reserpine action through the medium of the central sedative action of serotonin released in the brain is principally based upon the following evidence.

(1) Serotonin has a reserpine-like sedative action since it lengthens the sleeping time of barbiturate treated mice, similarly to reserpine (262). LSD shortened the prolonged sleeping time produced by both reserpine and serotonin (262).

(2) Reserpine causes a depletion of serotonin from the brain depots which outlasts the detectable concentrations of reserpine in the brain and parallels the duration of the reserpine sedation (129, 222).

(3) Serotonin releasing activity in confined to only those *Rauwolfia* alkaloids which also have central sedative action (41), although recently this action has been found to reside in certain benzoquinolizine derivatives which also appear to have sedative action (223).

The principal weakness of this theory seems to reside in the evidence cited above which suggests that the central sedative action of reserpine is mediated by the direct action of the serotonin. Other evidence suggests that serotonin may not have a tranquilizing but rather an excitatory function in the brain similar to other indole derivatives such as LSD, bufotenin, ibogaine, the harmala alkaloids and others. Although the sleeping time observations of Shore *et al.* (262) were confirmed by Brown (46), she found that these same doses produced radically different effects on the spontaneous activity of the mice. Instead of antagonism between serotonin and LSD, she observed a potentiation to increased activity from otherwise ineffective doses. Also there was no similarity to the interaction of reserpine with LSD compared to the combination of serotonin with LSD on activity measurements. Although the observed potentiation of barbiturate sleeping time by intraperitoneally injected serotonin may be correct, the interpretation of this as a central action is hazardous in view of the many unrelated substances which may affect this pharmacologic test (58, 169). Prolongation of mouse sleeping time has been shown to be better correlated with a hypothermic action of many drugs which may be either central or peripheral in mechanism (86, 178).

If serotonin has a central sedative action which is responsible for the action of reserpine one would expect that this would be potentiated by the joint administration of reserpine and the monoamine oxidase inhibitor, iproniazid, which would prevent the rapid metabolism of released serotonin. However, the administration of reserpine to iproniazid treated animals results in marked excitation (53, 266). This evidence seems to indicate a central excitant action for serotonin. It may explain the preliminary period of excitation or turbulence sometimes experienced by patients receiving sudden large amounts of reserpine. Further evidence for a central excitant action of serotonin comes from patients with metastatic malignant carcinoid who oftentimes show central excitation bordering on acute psychoses (196).

There are many experiments which have failed to show an antagonism between LSD and serotonin in the CNS and some of these have shown synergism between the two in causing the excitatory and peripheral sympathetic manifestations of LSD (79). In human beings only, chlorpromazine, of all the commonly used tranquilizers, fully blocked the actions of LSD (73). Chronic reserpine administration (0.5 mg. per kg.

i.m. daily for 7 days) markedly intensified the response to LSD and resulted in a catatonic-like state for 48 hours. The consistent pyretogenic effect of LSD was increased by the action of serotonin (137) when brain levels of this amine were increased by the administration of 5-hydroxytryptophan to iproniazid treated animals (282). The inhibitory action of serotonin on cortical synapses can be demonstrated by this same technique for increasing brain levels of serotonin (112).

Finally, there are many peripheral antagonists of serotonin other than LSD, such as atropine and D-2-Brom-LSD (BOL-148) which fail to have a hallucinogenic action on the brain although they penetrate the blood-brain barrier as well as does LSD (19, 51). Furthermore, D-2-Brom-LSD does not antagonize the reserpine effect on barbiturate anesthesia (49, 243).

The theory of Brodie has received some support from other laboratories. Woolley and Shaw (295) showed an antagonism between LSD and serotonin on the contractile activity of oligodendroglial cells in tissue culture, but they also observed synergistic actions of the two in producing contractions after the initial antagonism had passed. A similar antagonism was also observed by Geiger (110).

A depressant action of serotonin has been observed when it was injected into the brain ventricles of cats, but it was not antagonized by LSD (106, 251). The depressant action of serotonin was not reserpine-like in character and was more like a frightened immobility. An antagonism between intracerebrally injected LSD and serotonin was observed in mice (120). All of these brain injection studies are hampered by the question of whether serotonin diffuses to its normal site of action or exerts cerebrovascular effects to cause the observed actions.

In behavioral studies a depressant action of serotonin on conditioned reflexes has been observed which is antagonized by LSD (59, 292). This may not be representative of a central action of serotonin by reason of its failure to cross the blood-brain barrier (258).

Although there is no conclusive answer possible at present it appears to this reviewer that the preponderance of evidence favors a role for serotonin as a central excitatory agent at least in subcortical centers. The hyperactivity of serotonin rather than its deficiency may play a role in mediating uncontrolled emotional responses in acute psychoses. Thus the mechanism of reserpine action may be by depletion of brain concentrations of serotonin and/or certain catechol amines rather than through the sedative action of released serotonin. For this reason many studies are currently concerned with the urinary excretion and plasma levels of epinephrine and norepinephrine in psychiatric patients (74, 189, 231, 274), but with variable results likely because of the uncertainty of chemical methods available at present.

A very significant finding which correlates the activity of reserpine on rhinencephalic centers with the presence there of serotonin has been the discovery that contrary to earlier reports this indole exists in high concentrations in the limbic system, particularly the medial and prepyriform areas, the hippocampus, the amygdaloid and septal regions (211). Of further significance is an observed dependency of the conversion of 5-hydroxytryptophan to serotonin on an adequate dietary level of vitamin B_6 when one recalls the effects of pyridoxine deficiency on convulsive thresholds mentioned earlier (218).

Some suggestions have been made of an endocrine mode of action by reserpine (109). Evidence for a mild stimulant action on the pituitary-adrenal system has been found to be equivocal (19). Two recent reports, however, have shown increased 17-hydroxycorticoid excretion in monkeys (123) and in man (97). Depressions of metabolism have been reported which are likely peripheral rather than on the thyroid gland itself (66, 200).

Other effects on the sex glands are likely secondary to pituitary changes (280).

The peripheral effects of reserpine are generally conceded to be explained by the central reduction in sympathetic nervous outflow and a central blocking of sympathetic reflexes. The bradycardia, slight fall in blood pressure, miosis, hyperperistalsis and hypersecretion are thus caused by a reduction in the sympathetic stimulation to these organs and result in an apparent relative increase in parasympathetic function. Some transient cardiovascular side effects which are peripheral in origin have been ascribed to the releasing action of reserpine on serotonin and/or norepinephrine (198). Histamine release has also been described and may account for the commonly encountered nasal stuffiness (286). These peripheral side effects are annoying to anyone, but in mental patients they may cause even greater emotional upset and have been proposed as the cause of the severe depressions which may occur after prolonged therapy.

Although an increase in the gastric secretory response to test stimulation does occur (124), the basal gastric secretory rate is not increased with chronic administration (154, 232), and ulcers do not necessarily recur at a dosage rate of 0.75 mg. per day for 2 weeks (71).

The action of reserpine on spinal reflexes is disputed, with a claim of an increase in magnitude of monosynaptic reflex action (248) and a report of a selective depression of monosynaptic action potentials compared to polysynaptic pathways (165). This disagreement is likely a result of methodology and is not resolvable at present.

Rescinnamine. Rescinnamine has both sedative and hypotensive properties qualitatively similar to reserpine (61, 62). The relative potency of the two is close and comparisons vary in results depending upon the animal species tested (19).

Deserpidine (recanescine). This alkaloid also exerts similar sedative and hypotensive actions which in animals are qualitatively and quantitatively similar to reserpine. Clinical comparisons are available reporting superiority (92) and inferiority (107) for this drug in the treatment of psychiatric patients.

Phenothiazine Derivatives

Chlorpromazine. The development of chlorpromazine from a group of antihistaminic phenothiazines possessing unusually prominent central sedative actions has resulted in the evolution of a number of similar derivatives which are mostly devoid of their original histamine antagonism. This development has been related in the American literature by Koetschet (159). Chlorpromazine is outstandingly qualified for discussion as the prototype drug of this group by reason of wide experimental testing and extensive clinical trial. The tranquilizing action of this drug has been most effective in patients with some form of the schizophrenic reaction in which hyperactivity, agitation, hallucinations and marked anxiety are present. The large number of clinical impressions and discussions of this compound are beyond the scope of this review for tabulation (188).

In the brain, in addition to its blockade of hyperemotional responses, chlorpromazine exerts an antiemetic action, a hypotensive action on blood pressure regulating centers, a hypothermic action and in large doses some depression of respiration. Centrally it also exerts marked synergism with other CNS depressants and antagonizes stimulants to the brain. The onset of action of chlorpromazine is much more rapid than that for reserpine.

Peripherally it has been demonstrated to have an adrenergic blocking action, a cholinergic blocking action and an antihistaminic effect. However, these peripheral effects are not prominent in comparison with central mechanisms. The adrenergic blocking action has been shown to be feeble by studies in spinal animals (195) and in man (208). The cholinergic blocking action of

chlorpromazine has been estimated to be one-twenty-fifth to one-twenty-eighth that of promethazine. As an antihistaminic the compound is one-twenty-second to one-half as effective as that compound (246).

The tranquilizing action of chlorpromazine produces a state of lethargy, inactivity, a reduction of interest in the environment and a tendency toward drowsiness that is more prominent than for reserpine. This drowsiness is measurable in man as a lowering of the sedation threshold to intravenous amobarbital (40). There is a depression of conditioned reflexes at doses which do not affect the ability of the animal to escape from painful stimuli.

The EEG may reflect the hypoactivity by an increased slow wave activity and the appearance of spindles, but the effect is not marked (64, 130, 182, 237, 278, 279). Large doses produce an activating effect on the EEG similar to pentylenetetrazole (83, 197). It cannot be stated with certainty whether this is a direct neural effect or secondary to changes in cerebrovascular resistance which have been shown to occur simultaneously (144).

Many investigators have pointed to the ascending reticular activating system as the site of chlorpromazine blockage of arousal stimuli in curarized cats (130), unanesthetized cats (39) and in curarized rabbits (237). Large doses of chlorpromazine and other phenothiazine derivatives may also cause convulsive seizures or increase susceptibility to them (88). This may also be related to the stimulant effect of high doses on the mesodiencephalic activating system (226, 237). Other investigators have been unimpressed with the quantitative effect of chlorpromazine in these preparations (150, 203, 226, 279). Preston (226) found in curarized cats treated chronically with 10 mg. per kg. of chlorpromazine the initiation of spontaneous slow wave activity in the amygdaloid nucleus leading to seizures which extended to the cortex in larger doses. Delgado and Mihailovic have observed a similar finding in monkeys (68). Killam *et al.* (151) in unanesthetized cats without muscle immobilization did not find such an effect on spontaneous activity or electrode stimulations in this area. They did find a marked blocking effect of chlorpromazine on the EEG arousal and behavioral effects from electric stimuli placed in the nuclei of the diffuse thalamic projection system. Other experiments have shown the blockade by chlorpromazine of EEG desynchronization from stimuli located in the hypothalamic region (13, 182),

These neurophysiologic experiments are suggestive of a blocking action of chlorpromazine somewhere in the diencephalon. The clinical expression of this blocking action of the mesodiencephalic activating system seems to be the drowsiness or central sedative action. As will be seen later in certain phenothiazine derivatives this blocking action does not occur in proportion to a drug's blocking of conditioned avoidance responses to noxious stimuli. Himwich *et al.* (132) found difficulty in correlating depression of the reticular activating system with clinical potency in a series of phenothiazines. Bradley and Hance (39) and Rothballer (242) have suggested that this is a blockade of an adrenergic component of the mesodiencephalic activating system which is stimulated by epinephrine, norepinephrine, amphetamine and serotonin (although the action of the latter drug is not exactly similar to the sympathomimetics). Some human correlation to these results in animals has been obtained (255).

In contrast to reserpine, much less information is available on the biochemical nature of the chlorpromazine neural action. Most effects of the compound suggest it is primarily a depressant to cell activity. In the brain it accumulates in the lipide portions of neuronal cells, with the hypothalamus showing the highest concentrations of S^{35} from the labeled drug (54, 287). Studies of the effect of chlorpromazine on the oxygen consumption of cerebral cortex slices *in vitro*

have not been comparable to concentrations of the drug obtainable *in vivo* (28, 116, 205, 229) with the exception of one study (217). Studies of oxidative phosphorylation have revealed more sensitive effects by lower concentrations of the drug. Chlorpromazine appears to be a potent uncoupler of phosphorylation from oxidative respiration in liver mitochondria and to a lesser extent in brain mitochondria (1, 28). However, *in vivo* the effect of chlorpromazine is to cause an accumulation of ATP especially in the thalamic-hypothalamic region. This likely results as a reflection of the decreased energy utilization of these cells (116). Chlorpromazine also causes an increase in the accumulation of P^{32} in the phospholipides of brain slices (185) and in the phosphatides of mitochondria from brain cells (186). *In vivo* the turnover rate of rat brain phosphatides is depressed rather uniformly in all types of brain tissue by a large dose of chlorpromazine. Phosphatidylcholine is affected to a greater extent than phosphatidylethanolamine (5).

Chlorpromazine does not affect serotonin storage in tissues (42), but on test organs *in vitro* it demonstrates a potent serotonin blocking action (20, 27, 119).

The many peripheral actions of chlorpromazine have evoked much attention. The action on the cardiovascular system, which may be marked upon parenteral administration, is evidenced by a fall in blood pressure that is compensated by tachycardia. This is attributed to both a central depression of vasoregulatory reflexes and a peripheral adrenolytic action, the former being the more important. This hypotensive action is likely the basis of the antishock action of the compound similar to that found with other adrenergic blocking drugs like dibenamine (16, 127, 297).

Muscle tonus is depressed by chlorpromazine and, as observed in the early studies of "artificial hibernation" there is an antishivering action. This action is more likely a result of a central action on myotonic reflexes rather than a peripheral curare-like effect (161). Larger doses have a peripheral curarimimetic effect (160). Monosynaptic action potentials are claimed by one investigator (165) to be selectively depressed while another has found no effect on either monosynaptic or polysynaptic reflexes (226).

Another side effect of more chronic chlorpromazine therapy is the occurrence of jaundice in approximately 1 per cent of patients. The jaundice is of the intrahepatic cholestatic type and usually results in no associated hepatocellular damage (60). Its mechanism is uncertain. Increased resistance of the biliary sphincter mechanism has been suggested (202). Bile viscosity is not significantly raised (233). Other theories have implicated activation of a latent virus (148), allergy to chlorpromazine (291) and postulated interference in hepatic choline metabolism (214). Although bilirubin, thymol turbidity and Bromsulphalein tests often fail to warn of impending liver impairment, an increase in the serum oxalacetic aminopherase (transaminase) test may often detect approaching toxicity (149, 296). However, elevation of the serum oxalacetic transaminase test is caused by other causes, whereas the rise in alkaline phosphatase is more often a reflection of an obstructive type of jaundice (259).

Other side effects, dryness of the mouth, blurring of vision and constipation, are usually attributed to the atropine-like action of the drug. Many hormonal alterations may be produced by average to large doses of chlorpromazine. It produces supression of anterior pituitary function through its hypothalamic depression which results in amenorrhea and galactorrhea in women (7, 152, 275). In the pituitary-adrenal relationship it is suggested that chlorpromazine is a stress-producing drug causing evidences of increased adrenal cortex function (122, 166).

The most toxic side effect, which unfortunately is infrequent (0.001 to 0.002 per cent) is agranulocytosis (225). Its mech-

anism is unknown, but allergy to chlorpromazine has been suspected (244). Chlorpromazine, like reserpine, may cause a Parkinson-like tremor with a long dosage schedule. Women appear more susceptible to this side effect by a 2:1 ratio (101). This sign of extrapyramidal malfunction has been attributed to the effect of high doses on the mesodiencephalic activating system. It is relieved by the action of cholinergic blocking drugs of the atropine type which penetrate the blood-brain barrier, but not by quarternary derivatives of the methantheline type which do not cross. Larger doses produce a reversal of this depression and a stimulation of the reticular activating system which may produce convulsions with doses of chlorpromazine above 40 mg. per kg.

Other toxic effects are photosensitivity caused by the reaction of chlorpromazine in the skin to light and a dermatitis which may result from either the systemic effects of the drug (8) or through skin contact (172).

Promethazine. Though promethazine is most widely used for its antihistaminic, antinauseant and preanesthetic applications it has been recommended for the control of certain psychiatric disorders (77). However, the small series reported was not composed of many acute psychotics and a potency comparison to chlorpromazine was not made. It is likely that this compound may be considered when minimal hypotensive, hepatic and hematologic side effects are desired for the control of mild anxiety and tension.

Promazine. Promazine is approximately one-half as toxic as chlorpromazine in acute animal measurements (17). Its clinical potency in the management of acutely disturbed psychotics is also lower, but has not been well quantitated (87, 245). Orthostatic hypotension is less frequent with promazine (87). Agranulocytosis may occur (293), but the compound does not cause jaundice in experimental animals and so far none has been reported in man (252).

Mepazine. Mepazine in early studies in the United States showed high toxicity (155) which is now believed to be attributable to impurities (156). Bowes (38) believes this compound to be predominantly cholinergic blocking in its side effects since he noted no Parkinsonian tremor and little hypotension. Jaundice and blood dyscrasias may occur, as with chlorpromazine.

Prochlorperazine. Lower doses of prochlorperazine are more effective than chlorpromazine. The lethal effect of the compound is about one-half that of chlorpromazine and this ratio applies to the potency of the drug in side-by-side comparisons for most other pharmacologic actions except for the inhibition of conditioned reflexes and its antiemetic effect where it exceeds chlorpromazine by a large margin (143).

Perphenazine. This compound is claimed to exceed chlorpromazine sevenfold in its effect on behavioral activity (142). However, it was similar in potency in blocking the arousal of the mesodiencephalic activating system. This seems to indicate that this observation is not directly related to the action of the drug on conditioned avoidance responses. In man, 12 to 24 mg. per day have been reported to be effective for the treatment of anxiety, agitation and excitement (10). The drug is similar to other phenothiazines in the expected side effects except that blood dyscrasias, liver disorders and photosensitivity have been unreported in initial clinical trials (142).

Triflupromazine. Triflupromazine is a similar deviate in pharmacologic properties to perphenazine and prochlorperazine when compared to chlorpromazine. It is reported by its protagonists to be less toxic and to be more successful than chlorpromazine in suppressing conditioned avoidance responses, taming wild monkeys and in antiemetic action (48, 221).

Although many quantitative improvements in potency and decreased side effects have been gained by a study of other derivatives of phenothiazine, there appears to be little evidence of novel and unexpected properties among the group. In fact, the group

of compounds are remarkably similar in action and side effects.

Diphenyl Methane Derivatives

Azacyclonol. Azacyclonol occupies a unique position in the treatment of the schizophrenic psychoses. It has effects on the hallucinatory and confusional symptoms of the disease with little benefit in controlling the motor excitement and the autonomic emotional and physical changes (82, 209, 241). However, it is not successful in relieving the delusional aberrations in all schizophrenic dissociation syndromes. The attempts to obtain complete symptomatic control of schizophrenic symptoms may have led to the large number of negative reports concerning the use of this drug in unselected acute psychotics (21). This limitation in application has led the manufacturer to adopt the label of an antihallucinatory or anticonfusional drug rather than the tranquilizer title.

Azacyclonol is closely related chemically to the previously discussed CNS stimulating drug pipradrol (Meratran) in that only the position of the nitrogen atom in the piperazine ring has been changed.

Azacyclonol was first perceived to correct the experimentally induced hallucinations invoked by LSD and mescaline (81). It has few pharmacologic properties in common with other tranquilizing drugs except for the prolongation of barbiturate sleeping time (45). It will correct EEG abnormalities produced by LSD and mescaline but not pipradrol (235) although it will antagonize the hyperactivity produced by pipradrol and other CNS stimulants (45). The compound has a very low incidence of side effects. In acute toxicity tests large doses gave a pipradrol-like stimulation.

THE PSYCHONEUROTIC REACTIONS

For successful pharmacotherapy of the anxiety, tension, insomnia and other symptoms of psychoneurotic patients it is necessary that a drug be largely devoid of side effects. For this reason a large number of compounds having less tranquilizing potency, but with fewer autonomic and CNS side effects than the *Rauwolfia* and phenothiazine derivatives, have been applied mainly to the treatment of the psychoneuroses. The agents which have been used in this category of psychiatric therapy are shown in Table 2.

The drugs in Table 2 fall into these two categories on a chemical basis of classification. However, according to pharmacologic properties these drugs are quite heterogeneous. Included are drugs with spinal cord depressant, antihistaminic and anticholinergic properties in addition to their central actions.

Propanediol-Butanediol Derivatives

Meprobamate. Meprobamate is an outgrowth of efforts to prolong the transient action of mephenesin (Myanesin, Tolserol, Lissaphen, Relaxar, Glykresin, Oranixon, Toloxyn, Dioloxol, Siaan, Myodetensine).

TABLE 2

Drugs Used in the Therapy of Psychoneurotic Reactions

Generic Name	Proprietary Name	Pharmaceutical Firm
Propanediol—butanediol derivatives		
Meprobamate	Miltown	Wallace
	Equanil	Wyeth
Phenaglycodol	Ultran	Lilly
Diphenylmethane derivatives		
Benactyzine	Suavitil	Merck-Sharp & Dohme
Hydroxyzine	Atarax	Pfizer
Phenyltoloxamine	P.R.N.	Bristol
Doxylamine	Decapryn	Merrell

Mephenesin was shown to be metabolized quite rapidly to principally β-(1-toloxy)-lactic acid (234). Meprobamate is the result of an attempt to prolong the short action of a compound closely related to 2,2-diethylpropanediol (DEP, Prenderol), a spinal cord depressant similar in action to mephenesin by esterification with carbamic acid. Thus, meprobamate is the dicarbamate ester of 2-methyl-2-*n*-propyl-1,3-propanediol (23). In the CNS the compound was shown first to act as a spinal interneuronal depressant and thus as a muscle relaxant, especially in reflex states of muscle tension. It also exerted an anticonvulsant action (125). Later, largely as a result of its taming effect in monkeys given very large doses, it was introduced as a tranquilizer (24). Other studies suggestive of a central action showed the production of synchronization and a slow wave pattern in the EEG originating in the diencephalic region (125) and also in certain ganglia of the forebrain (24).

Berger (25) has reported that very large doses of meprobamate are necessary to affect the EEG in leads taken from the cortex. However, Pfeiffer *et al.* (220) showed the production of fast wave activity in humans with single oral doses of 1600 to 2000 mg. This they found was similar to the effects of secobarbital, phenobarbital and paraldehyde.

Meprobamate, because of its antipentylenetetrazole, antistrychnine and antielectroshock actions, has been recommended for the treatment of petit mal epilepsy (9, 216). Another barbiturate-like action is the production of grand mal seizures upon the sudden withdrawal of meprobamate after prolonged high dosage in mice (276) and in man (174). Other barbiturate-like properties include other withdrawal symptoms, psychologic dependency and tolerance (173).

Meprobamate has many pharmacologic differences from reserpine and chlorpromazine (27). It has no adrenolytic, anticholinergic or antihistaminic action. It has little enhancing action on the length of barbiturate induced sleep. It fails to inhibit the response of animals to conditioned reflexes short of doses which paralyze the animals' muscular capacity to respond. It has a greater depressant action on multisynaptic reflexes than for monosynaptic reflexes, but the action is not selective as previously believed (171). Although it is less potent than mephenesin in this respect (220) it is longer acting (27).

Thus the pharmacologic classification of meprobamate into previous categories is quite difficult. It appears to exert hybrid properties between mephenesin and certain of the barbiturates and/or trimethadione (220). Its greatest advantage is the low incidence of side effects, although these are now perceived to be more frequent than earlier studies indicated. They include drowsiness, hypersensitivity reactions and states of acute intoxication in addition to the withdrawal effects already mentioned.

Phenaglycadol. Phenaglycadol, 2-*p*-chlorophenyl-3-methyl,2,3-butanediol, resembles meprobamate in having persistent multisynaptic reflex depression, monkey taming action, antistrychnine activity, antipentylenetetrazole activity and a pentobarbital-like effect on the EEG although arousal stimuli were not blocked similarly to mephenesin (270). Thus, phenaglycadol appears to be, like meprobamate, another molecule with a cross between the properties of a spinal cord depressant and certain barbiturates and/or anticonvulsants. It also has been effective as an antiepileptic in petit mal seizures (118).

Diphenylmethane Derivatives

Benactyzine. Benactyzine has attracted widespread attention because of the unusual nature of its action. Its main usefulness has been in the treatment of psychoneuroses, but its side effects, though not dangerous, may be distracting to the overall clinical efficacy. The human effect of this drug is unique among the tranquilizers. The central relaxation is characterized by a block-

ing of recycling thought processes (rumination), difficulty in concentration and a slight hesitancy in speech (170). This has been substantiated by the finding of a significant lengthening of reaction time measurements in man (128). Other peculiar effects in man are a change in time perception, a heaviness of the limbs and a tendency to dizziness and ataxia caused apparently by the difficulty in concentration rather than any neuromuscular weakness. The drowsiness may also be a result of the decreased ability to concentrate and is more permissive rather than inductive of sleep.

A corollary of the drowsiness is a decrease in the α activity of the EEG (56, 128, 230). The pauses in the α activity of the EEG were unrelated to the normal inhibition of this activity by opening the eyes, thinking, hallucinations, etc. Whether these effects are reflective of lapses in consciousness and tension or the product of a central cholinergic blocking action cannot be stated as the origin of α activity is uncertain. Palmer has discounted the importance of these effects as an insignificant finding (212).

Benactyzine is fundamentally a cholinergic blocking drug with peripheral effects similar to the compound adiphenine (Trasentine, Ciba) to which it is closely related in chemical structure (170). It has mydriatic, antispasmodic and antisalivary effects typical of many other atropine-like drugs. Like some others of the atropine group it has antiParkinson properties (133). Similar to adiphenine it is also a local anesthetic. Benactyzine differs greatly from other tranquilizers in having none of the adrenolytic, antihistaminic or hypothermic effects of chlorpromazine. Although it causes heaviness of the limbs, unlike meprobamate, it has no interneuronal blocking action. It does not affect the metabolism of serotonin as does reserpine. The compound markedly lengthens the barbiturate sleeping time of animals (26).

Benactyzine, in contrast to atropine and adiphenine, has very potent effects on animal behavior. It abolishes the evidences of nervous tension in rats in a stressful situation (145). Differently from chlorpromazine, it facilitates simple, but depresses complicated reflexes (146). Thus, benactyzine, which affords unique properties among the tranquilizing drugs, may find new drug functions not yet recognized in the treatment of the psychoneuroses (136). In the general treatment of psychoneuroses, its overall effect is not striking (114).

Hydroxyzine. Drowsiness production is the predominant action of hydroxyzine which led to its use as a tranquilizer for mild states of anxiety and tension. The most marked peripheral pharmacologic action is its antihistaminic effect (180). Its chemical structure is closely related to a number of other antihistaminics, such as chlorcyclizine (Perazil, Perazyl, Di-Paralene, Histantine, AH-289). It is interesting that diphenhydramine (Benadryl, Amidryl), an antihistaminic with a large degree of sedative side effects and a similar chemical structure, produces a marked improvement in abnormal juvenile behavior (98). Hydroxyzine, like other tranquilizing drugs, lengthens the barbiturate sleeping time of animals and reduces their spontaneous motor activity (141). It has a slight action against adrenergic cardiovascular responses and as a cholinergic blocking drug is 0.2 per cent as active as atropine.

An almost complete lack of side effects except for drowsiness is an asset of this drug. Clinical reports have shown it to be effective principally in mild cases of anxiety and tension (57, 75, 84, 239, 256, 257).

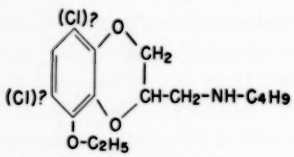
Phentoloxamine. Phentoloxamine resembles hydroxyzine in possessing antihistaminic action with a large central sedative component. Published clinical studies of its action as a tranquilizer are not yet available.

Doxylamine. This antihistaminic has also been reexamined for use as a tranquilizer (90). Although it produces drowsiness in a large portion of normal individuals it does

not appear to affect psychotic patients in this way even in large doses.

Miscellaneous Agents

Butamoxane. In agreement with the hypothesis of interference with cerebral adrenergic mechanisms as the mode of action of chlorpromazine, some compounds derived from the Fourneau series of adrenergic blocking agents related to piperoxan (Benodaine, 933-F) (96) have recently been described as tranquilizing drugs. It has been reported that ethoxy- and chlorethoxybutamoxane are 20 times more potent than chlorpromazine (210, 271, 285). The compound is unusual in that it antagonizes analgetics (238).



BUTAMOXANE - LILLY

Ectylurea. The compound ectylurea (2-ethyl-*cis*-crotonylurea, Nostyn-Miles-Ames) represents an attempt to identify a sedative with an as wide as possible margin between sedation as defined by reduced spontaneous activity and hypnosis as indicated by eye closure and sleep induction (181). It has been recommended for the treatment of anxiety and tension states (6, 91).

Cetadiol. Cetadiol (5-androstene-3,16-diol, Nepera) has been described as a steroidal tranquilizing agent. With the known anesthetic action of the steroid hydroxydione sodium (Viadril, Pfizer) and the central depressant action of other steroids including cholesterol (85), other steroids with tranquilizing action may well be anticipated.

SUMMARY

In concluding this review of the dynamically active field of the pharmacotherapy of mental disease one is tempted to point out three generalizations of drug action which appear to be crystallizing.

1. Mental depression may be related to either a neurohumoral deficiency of cerebral serotonin or some sympathomimetic amine or to some enzyme disorder such as a monoamine oxidase overactivity in the adrenergic excitatory mechanisms of the brain which might produce such a deficiency.

2. Drugs which are most effective in curbing the acute mania, motor excitement and hallucinations of the schizophrenic reaction are those which interfere in some manner with the adrenergic excitatory centers for emotional responses in the brain as exemplified by reserpine and chlorpromazine.

3. Psychoneurotic symptoms respond most favorably to drugs which have a minimum of side effects and produce a relaxation of neuromuscular tension and anxiety with a minimum of drowsiness and other symptoms of central nervous system depression.

REFERENCES

1. Abood, L. G. Effect of chlorpromazine on phosphorylation of brain mitochondria. Proc. Soc. Exp. Biol. & Med., **88:** 688–690, 1955.
2. Andren, H. E. Treatment of depression with Meratran and electroshock. Dig. Neurol. & Psychiat., **23:** 466, 1955.
3. Ann. New York Acad. Sc., Reserpine (Serpasil) and other alkaloids of *Rauwolfia serpentina*. Chemistry, pharmacology and clinical applications. **59:** 1–140, 1954.
4. Ann. New York Acad. Sc., Reserpine in the treatment of neuropsychiatric, neurological and related clinical problems. **61:** 1–280, 1955.
5. Ansell, G. B. and Dohmen, H. The depression of phospholipid turnover in brain tissue by chlorpromazine. J. Neurochem., **1:** 150–152, 1956.
6. Asung, C. L., Charcowa, A. I. and Villa, A. P. A study of the nonhypnotic calmative effect of 2-ethylcrotonylurea (Nostyn) in children with behavior problems. New York J. Med., **57:** 1911–1914, 1957.
7. Ayd, F. J. Thorazine and Serpasil treatment of private neuropsychiatric patients. Am. J. Psychiat., **113:** 16–21, 1956.
8. Ayd, F. J., Jr. The dermatological and systemic manifestations of chlorpromazine hypersensitivity. J. Nerv. & Ment. Dis., **124:** 84, 1956.
9. Ayd, F. J., Jr. Meprobamate therapy for con-

vulsive disorders of children. Bull. School Med. Univ. Maryland, **42**: 2–5, 1957.

10. Ayd, F. J. The treatment of anxiety, agitation and excitement in the aged. A preliminary report of Trilafon. J. Am. Geriatrics Soc., **5**: 92–96, 1957.
11. Azima, H. Report on the international colloquium on chlorpromazine and neuroleptic medications in psychiatric treatment, Paris, October 20–27, 1955. Am. J. Psychiat., **112**: 749–750, 1956.
12. Baird, H. W., Szekely, E. G., Wycis, H. T. and Spiegel, E. A. The effect of meprobamate on the basal ganglia. Ann. New York Acad. Sc., **67**: 873–884, 1957.
13. Barraclough, C. A. Blockade of the release of pituitary gonadotrophin by chlorpromazine. Anat. Rec., **124**: 255, 1956.
14. Barraclough, C. A. and Sawyer, C. H. Blockade of the release of pituitary ovulating hormone in the rat by chlorpromazine and reserpine. Possible mechanism of action. Endocrinology, **61**: 341, 1957.
15. Barsa, J. A. The dual action of tranquilizers. Am. J. Psychiat., **114**: 74–75, 1957.
16. Beck, L. V. and Redict, T. F. Chlorpromazine on tourniquet trauma in mice. Am. J. Physiol. (Proc.), **183**: 596, 1955.
17. Begany, A. J., Seifter, J., Pless, H. H., Huber, R. deV. and Bruce, W. F. Tranquilizing effect of phenothiazines in cats and rabbits. Fed. Proc., **15**: 399–400, 1956.
18. Begg, W. G. A. and Reid, A. A. Meratran. A new stimulant drug. Brit. M. J., **1**: 946–949, 1956.
19. Bein, H. J. The pharmacology of *Rauwolfia*. Pharmacol. Rev., **8**: 435–483, 1956.
20. Benditt, E. P. and Rowley, D. A. Antagonism of 5-hydroxytryptamine by chlorpromazine. Science, **123**: 24, 1956.
21. Bennett, I. F. The tranquilizers. J. Am. Pharm. A. (Pract. Ed.), **18**: 547–550, 1957.
22. Bente, D. and Itil, T. The effects of high-dosed reserpine (Serpasil) treatment and drug-induced parkinsonism-like states on the electroencephologram. Med. klin., **50**: 1296–1301, 1955.
23. Berger, F. M. The anticonvulsant activity of carbamate esters of certain 2,2-disubstituted-1,3-propanediols. J. Pharmacol. & Exper. Therap., **104**: 229–233, 1952.
24. Berger, F. M. The pharmacological properties of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (Miltown). A new interneuronal blocking agent. J. Pharmacol. & Exper. Therap., **112**: 413, 1954.
25. Berger, F. M. Meprobamate. Its pharmacologic properties and clinical usage. Internat. Rec. Med., **169**: 184–196, 1956.
26. Berger, F. M., Hendley, C. D. and Lynes, T. E. Pharmacology of the psychotherapeutic drug Benactyzine (β-diethyl aminoethyl benzilate hydrochloride). Proc. Soc. Exp. Biol. & Med., **92**: 563, 1956.
27. Berger, F. M. The chemistry and mode of action of tranquilizing drugs. Ann. New York Acad. Sc., **67**: 685–700, 1957.
28. Berger, M., Strecker, H. J. and Waelsch, H. Action of chlorpromazine on oxidative phosphorylation of liver and brain mitochondria. Nature, London, **177**: 1234–1235, 1956.
29. Bernsohn, J., Namajuska, I. and Cochrane, L. S. G. The effect of chlorpromazine on respiration and glycolysis in rat brain. Arch. Biochem., **62**: 274–283, 1956.
30. Bhargava, K. P. and Borison, L. H. Effects of *Rauwolfia* alkaloids on hypothalamic, medullary and spinal vasoregulatory systems. J. Pharmacol. & Exper. Therap., **115**: 464, 1955.
31. Bianchi, C. Reserpine and serotonin in experimental convulsions. Nature, London, **179**: 202–203, 1957.
32. Blaschko, H. Amine oxidase and amine metabolism. Pharmacol. Rev., **4**: 415, 1952.
33. Bleuler, M. Psychiatric errors in serotonin research. Deutsche med. Wchnschr., **81**: 1078–1081, 1956.
34. Bogdanski, D. F. and Udenfriend, S. Serotonin and monoamine oxidase in brain. J. Pharmacol. & Exper. Therap., **116**: 7, 1956.
35. Bogdanski, D. F., Weissbach, H. and Udenfriend, S. The distribution of serotonin, 5-hydroxytryptophan decarboxylase and monoamine oxidase in brain. J. Neurochem., **1**: 272–278, 1957.
36. Bonneycastle, D. D. Giarman, N. J. and Paasonen, M. K. Anticonvulsant compounds and 5-hydroxytryptamine in rat brain. Brit. J. Pharmacol., **12**: 228–231, 1957.
37. Borrus, J. C. Study of effect of Miltown (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate) on psychiatric states. J. A. M. A., **157**: 1596–1598, 1955.
38. Bowes, H. A. The ataractic drugs. The present position of chlorpromazine, Frenquel, Pacatal and reserpine in the psychiatric hospital. Am. J. Psychiat., **113**: 530–539, 1956.
39. Bradley, P. B. and Hance, A. J. The effect of chlorpromazine and methopromazine on the electrical activity of the brain in the cat. Electroencephalog. & Clin. Neurophysiol., **9**: 191–215, 1954.
40. Bradley, P. B. and Jeavons, P. M. The effect of chlorpromazine and reserpine on sedation and convulsive thresholds in schizophrenic patients. Electroencephalog. & Clin. Neurophysiol., **9**: 661–672, 1957.
41. Brodie, B. B., Shore, P. A. and Pletscher, A. Serotonin-releasing activity limited to *Rauwolfia* alkaloids with tranquilizing action. Science, **123**: 992–993, 1956.
42. Brodie, B. B. and Shore, P. A. A concept for a role of serotonin and norepinephrine as chemical mediators in the brain. Ann. New York Acad. Sc., **66**: 631–642, 1957.
43. Brodie, B. B., Tomich, E. G., Kuntzman, R.

AND SHORE, P. A. On the mechanism of action of reserpine. Effect of reserpine on capacity of tissues to bind serotonin. J. Pharmacol. & Exper. Therap., **119:** 461, 1957.

44. BROWN, B. B. AND WERNER, H. W. Pharmacologic studies on a new central stimulant, α-(2-piperidyl) benzhydrol hydorchloride (MRD)-108). J. Pharmacol. & Exper. Therap., **110:** 180–187, 1954.
45. BROWN, B. B., BRAUN, D. L. AND FELDMAN, R. G. The pharmacologic activity of α-(4-piperidyl)-benzhydrol hydrochloride (Azacyclonal hydrochloride). An ataractive agent. J. Pharmacol. & Exper. Therap., **118:** 153, 1956.
46. BROWN, B. B. Lysergic acid diethylamide antagonism of certain drugs. Ann. New York Acad. Sc., **66:** 677–685, 1957.
47. BURGER, M. Decrease of the plasma noradrenaline concentration by reserpine. Helvet. physiol. et pharmacol. acta., **14:** C13–14, 1956.
48. BURKE, J. C., HASSERT, G. L. AND HIGH, J. P. The tranquilizing activity of 10-(3-dimethyl-aminopropyl)-2-(trifluoromethyl)-phenothiazine hydrochloride (MC-4703) and related phenothiazines in animals. J. Pharmacol. & Exper. Therap., **119:** 136, 1957.
49. BURTON, R. M. The analeptic action of lysergic acid diethylamide on reserpine-sedated mice. Ann. New York Acad. Sc., **66:** 695–697, 1957.
50. CARLSSON, A. AND HILLARP, N. Release of adrenaline from the adrenal medulla of rabbits produced by reserpine. Kgl. Fysiograf. Sällskap. Lund Förh., **26:** 90–91, 1956.
51. CERLETTI, A. AND ROTHLIN, E. Role of 5-hydroxytryptamine in mental diseases and its antagonism to lysergic acid derivatives. Nature, London, **176:** 785–786, 1955.
52. CHEN, G., ENSOR, C. R. AND BOHNER, B. A facilitation action of reserpine on the central nervous system. Proc. Soc. Exper. Biol. & Med., **86:** 507–510, 1954.
53. CHESSIN, M., KRAMER, E. R. AND SCOTT, C. C. Modification of the pharmacology of reserpine by iproniazid. J. Pharmacol. & Exper. Therap., **119:** 453–460, 1957.
54. CHRISTENSEN, J. AND WASE, A. W. Distribution of S^{35} in the mouse after administration of S^{35} 10-(dimethylaminopropyl)-2-chlorophenothiazine (chlorpromazine). Acta pharmacol. et toxicol., **12:** 81–84, 1956.
55. CLARK, L. D. Evaluation of the therapeutic effects of drugs in psychiatric patients. Dis. Nerv. System, **17:** 282–286, 1956.
56. COADY, A. AND JEWESBURY, E. C. O. A clinical trial of benactyzine hydrochloride (Suavitil) as a psychical relaxant. Brit. M. J., **1:** 485–487, 1956.
57. COIRAULT, R., SCHULLER, E. AND PERIER, M. A. sedative for the daily practice. Hydroxyzine. Presse méd., **64:** 2239–2240, 1957.
58. COOK, D. L., TONER, J. J. AND FELLOWS, E. J. The effect of β-diethylaminoethyldiphenylpropyl-acetate hydrochloride (SKF No. 525-A) on Hexobarbital. J. Pharmacol. & Exper. Therap., **111:** 131–141, 1954.
59. COOK, L. AND WEIDLEY, E. Behavioral effects of some psychopharmacological agents. Ann. New York Acad. Sc. **66:** 740–752, 1957.
60. CRADDOCK, W. L. Toxic effects of chlorpromazine. U. S. Armed Forces M. J., **72:** 1726–1740, 1956.
61. CRONHEIM, G., BROWN, W., CAWTHORNE, J., TOEKES, M. I. AND UNGARI, J. Pharmacological studies with rescinnamine, a new alkaloid isolated from *Rauwolfia serpentina*. Proc. Soc. Exper. Biol. & Med., **86:** 120–124, 1954.
62. CRONHEIM, G. AND TOEKES, M. I. Comparison of some pharmacological properties of rescinnamine and reserpine, two alkaloids isolated from *Rauwolfia serpentina*. J. Pharmacol. & Exper. Therap., **113:** 13, 1955.
63. CRONHEIM, G. The reserpine-serotonin interrelation in the central nervous system. Proc. XX Internat. Physiol. Cong., Brussels, pp. 204–205, 1956.
64. DAS, N. N., DASGUPTA, S. R. AND WERNER, G. Changes of behaviour and electroencephalogram in rhesus monkeys caused by chlorpromazine. Arch. internat. pharmacodyn., **99:** 451–457, 1954.
65. DAVIDOFF, E., BEST, J. L. AND MCPHEETERS, H. L. The effect of Ritalin (methyl-phenidyl-acetate hydrochloride) on mildly depressed ambulatory patients. New York J. Med., **57:** 1753, 1957.
66. DE FELICE, E. A., SMITH, T. C. AND DEARBORN, E. H. Effect of reserpine (Serpasil) on oxygen consumption of euthyroid, hypothyroid, and hyperthyroid guinea pigs. Proc. Soc. Exper. Biol. & Med., **94:** 171–175, 1957.
67. DELAY, J., PICHOT, P. AND ROPERT, R. A new neurolistic medication in psychiatry. The acid maleate of ethylone-3-dimethylamino-3′-propyl-10-phenothiazine, 1522-CB. Presse méd., **65:** 491–493, 1957.
68. DELGADO, J. M. R. AND MIHAILOVIC, L. Use of intracerebral electrodes to evaluate drugs that act on the central nervous system. Ann. New York Acad. Sc., **64:** 644–666, 1956.
69. DELL, P., BONVALLET, M. AND HUGELIN, A. Sympathetic tonus, adrenaline and the reticular control of spinal motricity. Electroencephalog. & Clin. Neurophysiol., **6:** 599–618, 1954.
70. DELL, P. AND BONVALLET, M. The control action of adrenaline. Pharmacological consequences. Electroencephalog. & Clin. Neurophysiol., **8:** 701, 1956.
71. DRENICK, E. J. Reserpine in peptic ulcer. Am. J. Digest. Dis., **1:** 521–525, 1956.
72. EDWALDS, R. M. Intravenous administration of PM-1090. Clinical experience with a new convulsant drug. Proc. New York Divisional

Meeting, American Psychiatric Assoc., New York, Nov. 16, 1957, to be published.

73. Elder, J. T., Jr., Gogerty, J. H. and Dille, J. M. Survey of D-lysergic acid diethylamide (LSD) antagonists. Fed. Proc., **16:** 293–294, 1957.
74. Elmadjian, F., Hope, J. M. and Lamson, E. T. Excretion of epinephrine and norepinephrine in various emotional states. J. Clin. Endocrinol., **17:** 608–620, 1957.
75. Ende, M. Clinical evaluation of Atarax. Virginia M. Month., **83:** 503–505, 1956.
76. Erspamer, V. Pharmacological studies on Enteramine (5-hydroxytryptamine). IX. Influence of sympathomimetic and sympatholytic drugs on the physiological and pharmacological actions of Enteramine. Arch. internat. pharmacodyn., **93:** 293–316, 1953.
77. Erwin, H. J. Clinical observations on the use of promethazine hydrochloride in psychiatric disorders. Am. J. Psychiat., **113:** 783–787, 1957.
78. Esquibel, A. Krantz, J. C., Jr., Truitt, E. B., Jr. and Kurland, A. A. The use of hexafluorodiethyl ether (Indoklon) as an inhalant convulsant. Am. J. Psychiat., **114:** 461, 1957.
79. Evarts, E. F. A review of the neurophysiological effects of lysergic acid diethylamide (LSD) and other psychotomimetic agents. Ann. New York Acad. Sc., **66:** 479–495, 1957.
80. Fabing, H. D., Hawkins, J. R. and Moulton, J. A. L. Clinical studies on α-(2-piperidyl) benzhydrol hydrochloride, a new anti-depressant drug. Am. J. Psychiat., **111:** 832–836, 1955.
81. Fabing, H. D. New blocking agent against the development of LSD-25 psychosis. Science, **121:** 208–209, 1955.
82. Fabing, H. D. and Hawkins, J. R. A year's experience with Frenquel in clinical and experimental psychoses. Dis. Nerv. System, **16:** 329–338, 1955.
83. Fabisch, W. The effect of intravenous chlorpromazine on the EEG of epileptic patients. Electroencephalog. & Clin. Neurophysiol., **8:** 712, 1956.
84. Farah, L. Preliminary study on the use of Hydroxyzine in psychosomatic affections. Internat. Rec. Med., **169:** 379–389, 1956.
85. Farson, DeC. B., Carr, C. J. and Krantz, J. C., Jr. Anesthesia. XXI. Anesthesia and the steroid hormones. Proc. Soc. Exper. Biol. & Med., **63:** 70–71, 1946.
86. Fastier, F. N., Speden, R. N. and Waal, H. Prolongation of chloral hydrate sleeping time by 5-hydroxytryptamine in the rat. Brit. J. Pharmacol., **12:** 251, 1957.
87. Fazekas, J. F., Schultz, J. D., Sullivan, P. D. and Shea, J. G. Management of acutely disturbed patients with Promazine (Sparine). J. A. M. A., **161:** 46–49, 1956.
88. Fazekas, J. F., Shea, J. G., Ehrmantraut, W. R. and Alman, R. W. Convulsant action of phenothiazine derivatives. J. A. M. A., **165:** 1241–1245, 1957.
89. Ferguson, J. T. Treatment of reserpine-induced depression with a new analeptic. Phenidylate. Ann. New York Acad. Sc., **61:** 101–107, 1955.
90. Ferguson, J. T. Doxylamine. A new compound for the symptomatic treatment of schizophrenia. J. Nerv. & Ment. Dis., **124:** 377–380, 1956.
91. Ferguson, J. T. and Linn, F. V. Z. A new compound for the symptomatic treatment of tension and anxiety. 2-ethylcrotonylurea (Nostyn). Antibiot. Med., **3:** 329–333, 1956.
92. Ferguson, J. T. Comparison of reserpine and harmonyl in psychiatric patients. A preliminary report. Lancet, **76:** 389–390, 1956.
93. Florey, E. and Florey, E. 5-hydroxytryptamine as nerve action substance for cephalopoda and decapod crustaceae. Naturwissenschaften, **15:** 413–414, 1953.
94. Forrer, G. R. Symposium on atropine toxicity therapy. History and future research. J. Nerv. & Ment. Dis., **124:** 256–259, 1956.
95. Forster, W., Henderson, L. and Schultz, S. The clinical effects of alpha-(2-piperidyl)-benzhydrol hydrochloride (Meratran) in states of inactivity in elderly psychiatric patients. Dig. Neurol. & Psychiat., **23:** 278, 1955.
96. Fourneau, E. and Bovet, D. Sympathicolytic action of diethylaminoethyl benzodioxane, a new derivative. Arch. internat. pharmacodyn., **46:** 178–191, 1933.
97. Fraser, H. F., Eisenman, A. J. and Brooks, J. W. Urinary excretion of 5 HIAA and corticoids after morphine, meperidine, nalorphine, reserpine, and chlorpromazine. Fed. Proc. **16:** 298, 1957.
98. Freedman, A. M., Effron, A. S. and Bender, L. Pharmacotherapy in children with psychiatric illness. J. Nerv. & Ment. Dis., **122:** 479–486, 1955.
99. Freeman, H. A critique of the tranquilizing drugs, chlorpromazine and reserpine, in neuropsychiatry. New England J. M., **255:** 877–883, 1956.
100. Freyberger, W. A., Graham, B. E., Rapport, M. M., Seay, P. H., Govier, W. M., Swoap, O. F. and Vanderbrook, M. J. The pharmacology of 5-hydroxytryptamine (serotonin). J. Pharmacol. & Exper. Therap., **105:** 80–86, 1952.
101. Freyhan, F. A. Therapeutic implications of differential effects of new phenothiazine compounds. Proc. New York Divisional Meet., Am. Psychiat. Assoc., New York, Nov. 16, 1957, to be published.
102. Frommel, E. and Gold, P. Sites of action of the total alkaloids of *Rauwolfia* and reserpine on the sleep center. Acta pharmacol. et toxicol., **13:** 345–356, 1957.
103. Fulton, J. F. *Physiology of the Nervous Sys-*

tem, Ed. 2. Oxford University Press, New York, 1943, p. 248.

104. Gaddum, J. H. Ciba Foundation Symposium on Hypertension. Little, Brown & Company, Boston, Mass., 1954, p. 75.
105. Gaddum, J. H. and Hameed, K. A. Drugs which antagonize 5-hydroxytryptamine. Brit. J. Pharmacol., **9:** 240–248, 1954.
106. Gaddum, J. H. and Vogt, M. Central actions of 5-hydroxytryptamine and various antagonists. Brit. J. Pharmacol., **11:** 175–179, 1956.
107. Gallagher, W. J., Berry, J. M., Dierden, W. D. and Lazanby, W. D. Comparative study of reserpine, 11-desmethoxyreserpine and *Rauwolfia* alkaloids in treatment of schizophrenia. In *Tranquilizing drugs*. (H. E. Himwich, editor). Publication 46. AAAS 133–147, Washington, D.C., 1957.
108. Gastaut, H. Combined photic and Metrazol activation of the brain. Electroencephalog. & Clin. Neurophysiol., **2:** 249–261, 1950.
109. Gaunt, R., Renzi, A. A., Antonchak, N., Miller, G. J. and Gilman, M. Endocrine aspects of the pharmacology of reserpine. Ann. New York Acad. Sc., **59:** 22–35, 1954.
110. Geiger, R. S. Effect of lysergic acid diethylamide (LSD-25) and serotonin on adult cortical brain cells in tissue culture. Fed. Proc., **16:** 44–45, 1957.
111. Gertner, S. B., Paasonen, M. K. and Giarman, N. J. Presence of 5-hydroxytryptamine (serotonin) in perfusate from sympathetic ganglia. Fed. Proc., **16:** 299, 1957.
112. Gluckman, M. I., Hart, E. R. and Marrazzi, A. S. Cerebral synaptic inhibition by serotonin and iproniazid. Science, **126:** 448–449, 1957.
113. Goar, E. L. and Fletcher, M. C. Toxic chorioretinopathy following the use of NP-207. Am. J. Ophthalmol., **44:** 603, 1957.
114. Gore, C. P. and Walton, D. Benactyzine in the treatment of anxiety and tension. Lancet, **2:** 294, 1957.
115. Govier, W. M., Howes, B. G. and Gibbons, A. J. The oxidative deamination of serotonin and other 3-(β-aminoethyl) indoles by monamine oxidase and the effect of these compounds on the determination of tyramine. Science, **118:** 596–597, 1953.
116. Grenell, R. G., Mendelson, J. and McElroy, W. D. Effects of chlorpromazine on metabolism in central nervous system. A. M. A. Arch. Neurol. & Psychiat., **73:** 347–351, 1955.
117. Griesemer, E. C., Barsky, J., Dragstedt, C. A., Wells, J. A. and Zeller, E. A. Potentiating effect of iproniazid on the pharmacological action of sympathomimetic amines. Proc. Soc. Exper. Biol. & Med., **84:** 699–701, 1953.
118. Gruber, C. M., Jr. and Mosier, J. M. Phenaglycodol. A new antiepileptic agent. Proc. Soc. Exper. Biol. & Med., **94:** 384–385, 1957.
119. Gyermek, L., Lazar, I. and Csak, A. Z. The antiserotonin action of chlorpromazine and some other phenothiazine derivatives. Arch. internat. pharmacodyn., **107:** 62–74, 1956.
120. Haley, T. J. 5-hydroxytryptamine antagonism by lysergic acid diethylamide after intracerebral injection in conscious mice. J. Am. Pharm. A. (Scient. Ed.), **46:** 428–430, 1957.
121. Harrison, F. and Goth, A. Effect of reserpine on the hypothalamic pressor response. J. Pharmacol. & Exper. Therap., **116:** 262–267, 1956.
122. Harwood, T. C. and Mason, J. W. Effect of tranquilizing agents on ACTH secretion. Proc. XX Internat. Physiol. Cong., Brussels, 1956, p. 402
123. Harwood, T. C. and Mason, J. W. Acute effects of tranquilizing drugs on the anterior pituitary—ACTH mechanism. Endocrinology, **60:** 239–246, 1957.
124. Haverback, B. J., Stevenson, T. D., Sjoerdsma, A. and Terry, L. L. The effects of reserpine and chlorpromazine on gastric secretion. Am. J. M. Sc., **230:** 601–604, 1955.
125. Hendley, C. D., Lynes, T. E. and Berger, F. M. Effect of 2-methyl, 2-*n*-propyl-1,3-propanediol dicarbamate (Miltown) on central nervous system. Proc. Soc. Exper. Biol. & Med., **87:** 608–610, 1954.
126. Hendley, C. D. Effects of SCH 3940 and methyl-pentynyl carbamate on electrical activity of the brain. Comparison with other CNS depressants. Fed. Proc., **16:** 306, 1957.
127. Hershey, S. G., Zweifach, B. W. and Antopol, W. Factors associated with protection against experimental shock. Anesthesiology, **17:** 265–276, 1956.
128. Hess, G. and Jacobsen, E. The influence of benactyzine on reaction time. Acta pharmacol. et toxicol., **13:** 135–141, 1957.
129. Hess, S. M., Shore, P. A. and Brodie, B. B. Persistence of reserpine action after the disappearance of drug from brain. Effect on serotonin. J. Pharmacol. & Exper. Therap., **118:** 84–89, 1956.
130. Hiebel, G., Bonvallet, M. and Dell, P. Effects of chlorpromazine on central nervous system. Semaine hôp. Paris, **30:** 2345–2346, 1954.
131. Himwich, H. E. and Rinaldi, F. An analysis of the activating system including its use for screening anti-Parkinson drugs. Yale J. Biol. & Med., **28:** 308–319, 1955–1956.
132. Himwich, H. E., Rinaldi, F. and Willis, D. An examination of phenothiazine derivatives with comparisons of their effects on the alerting reaction. Chemical structure and therapeutic efficiency. J. Nerv. & Ment. Dis., **124:** 53–57, 1956.
133. Himwich, H. E. and Rinaldi, F. The anti-Parkinson activity of benactyzine. Arch. internat. pharmacodyn., **110:** 119–127, 1957.
134. Hoffer, A. and Kenyon, M. Conversion of

adrenaline to adrenolutin in human blood serum. A. M. A. Arch. Neurol. & Psychiat., **77:** 437–438, 1957.

135. Holzbauer, M. and Vogt, M. Depression by reserpine of the noradrenaline concentration in the hypothalamus of the cat. J. Neurochem., **1:** 8–11, 1956.
136. Hopkins, S. J. Benactyzine and psychoneurosis. Pharm. J., London, **176:** 333, 1956.
137. Horita, A. and Gogerty, J. H. Comparison of pyretogenic action of 5-hydrotryptophan (HTP) and lysergic acid diethylamide (LSD). Fed. Proc., **16:** 308, 1957.
138. Horwitz, B. S. and Wang, S. C. Reserpine effect in medullary vasomotor mechanism of the cat. Fed. Proc., **15:** 439–440, 1956.
139. Houston, F. Group behavior in chronic schizophrenics treated with Meratran. Brit. M. J., **1:** 949–952, 1956.
140. Huguenard, P. Clinical study of a new neuroplegic, 1522-CB (acetylpromazine maleate). Presse méd., **65:** 685–688, 1957.
141. Hutcheon, D. E., Scribiane, A. and Schrogie, J. J. Pharmacology of hydroxyzine, a new tranquilizing drug. J. Pharmacol. & Exper. Therap., **119:** 154, 1957.
142. Information supplied by Schering Corp., 1957.
143. Information supplied by Smith, Kline & French Co., Dec., 1956.
144. Ingvar, D. H. and Soderberg, U. Effects of chlorpromazine on cerebral circulation and electroencephalogram in cats. A. M. A. Arch. Neurol. & Psychiat., **78:** 254–258, 1957.
145. Jacobsen, E. and Sonne, E. The effect of benzilic acid diethylaminoethylester HCl (Benactyzine) on stress-induced behaviour in the rat. Acta pharmacol. et toxicol., **11:** 135–147, 1955.
146. Jacobsen, E. and Sonne, E. The effect of Benactyzine on the conditioned responses in the rat. Acta. pharmacol. et toxicol., **12:** 310–320, 1956.
147. Jasper, H. Diffuse projection systems. The integrative action of the thalamic reticular system. Electroencephalog. & Clin. neurophysiol., **1:** 405–420, 1949.
148. Johnson, H. C., Jr. and Doenges, J. P. Intrahepatic obstructive jaundice (primary cholestasis), a clinicopathologic syndrome of varied etiology. A review with observations of the use of corticotrophin as a diagnostic tool. Ann. Int. Med., **44:** 589–616, 1956.
149. Kessler, G., Halpern, P. and Brody, H. Serial serum glutamic oxalacetic transaminase (SGOT) and electrophoresis studies in thorazine-induced jaundice. J. Lab. & Clin. Med., **50:** 250–256, 1957.
150. Killam, E. K. and Killam, K. F. A comparison of the effects of reserpine and chlorpromazine to those of barbiturates on central afferent systems in the cat. J. Pharmacol. & Exper. Therap., **116:** 35, 1956.
151. Killam, K. F., Killam, E. K. and Shaw, T. The effects of psychotherapeutic compounds on central afferent and limbic pathways. Ann. New York Acad. Sc., **66:** 784–805, 1957.
152. Kinross-Wright, V. Complications of chlorpromazine treatment. Dis. Nerv. System, **16:** 114–119, 1955.
153. Kinross-Wright, V. Clinical trial of a new phenothiazine compound. NP-207. Psychiat. Res. Rep., **4:** 89–94, 1956.
154. Kirsner, J. B. and Ford, H. The effect of reserpine upon basal gastric secretion in man. A. M. A. Arch. Int. Med., **99:** 390–400, 1957.
155. Kline, N. S. and Jacobs, G. M. Use of Pacatal (*N*-methylpiperidyl-(3) methylphenothiazine) in psychiatric patients. Am. J. Psychiat., **112:** 63, 1955.
156. Kline, N. S. Letter to the editor. Am. J. Psychiat., **113:** 565, 1956.
157. Klüver, H. and Bucy, P. C. Preliminary analysis of functions of temporal lobes in monkeys. A. M. A. Arch. Neurol. & Psychiat., **42:** 979–1000, 1939.
158. Koelle, G. B. and Valk, A. deT., Jr. Physiological implications of the histochemical localization of monamine oxidase. J. Physiol., London, **126:** 434–447, 1954.
159. Koetschet, P. Can it be said that chlorpromazine has specific properties? Internat. Rec. Med., **168:** 295–300, 1955.
160. Kopera, J. and Armitage, A. K. Comparison of some pharmacological properties of chlorpromazine, promethazine and pethidine. Brit. J. Pharmacol., **9:** 392–401, 1954.
161. Kotkin, S., Lear, E., Chiron, A. E., Pallin, I. M. and Dickler, D. Preliminary studies on the muscle relaxing properties of chlorpromazine. Anesthesiology, **17:** 494–499, 1956.
162. Kraines, S. H. *Mental Depressions and Their Treatment.* Macmillan Company, New York, 1957, p. 448.
163. Krantz, J. C., Jr., Truitt, E. B., Jr., Speers, L. and Ling, A. S. C. New pharmacoconvulsive agent. Science, **126:** 353–354, 1957.
163-A. Krantz, J. C., Jr., Truitt, E. B., Jr., Ling, A. S. C. and Speers, L. Anesthesia LV. The pharmacologic response to hexafluorodiethyl ether. J. Pharmacol. & Exper. Therap., **121:** 362–368, 1957.
164. Krantz, J. C., Jr., Esquibel, A., Truitt, E. B., Jr., Ling, A. S. C. and Kurland, A. A. Hexaflurodiethyl ether (Indoklon) a volatile convulsant—its use in psychiatric treatment. J. A. M. A., in press.
165. Krivoy, W. A. Actions of chlorpromazine and of reserpine on spinal reflex activity in the cat. Proc. Soc. Exper. Biol. & Med., **96:** 18, 1957.
166. Kovacs, K., Horvath, E., Kovacs, B. M., Kovacs, G. S. and Petri, G. The influence

of chlorpromazine on the changes of the adrenal cortex caused by hypertonic saline in the rats. Arch. internat. pharmacodyn., **108:** 170–179, 1956.

167. Kurland, A. A. Comparison of chlorpromazine and reserpine in treatment of schizophrenia. A. M. A. Arch. Neurol. & Psychiat., **75:** 510–513, 1956.
168. Kurland, A. A. The drug placebo. Its psychodynamic and conditional reflex action. Behavioral Sc., **2:** 101–110, 1957.
169. Lamson, P. D., Greig, M. E. and Williams, L. Potentiation by epinephrine of the anesthetic effect in chloral and barbiturate anesthesia. J. Pharmacol. & Exper. Therap., **106:** 219–225, 1952.
170. Larson, V. The general pharmacology of benzilic acid diethyl aminoethylester hydrochloride (Benactyzine NFD, Suavitil, Parasan). Acta pharmacol. et toxicol., **11:** 405–420, 1955.
171. Latimer, C. N. The action of mephenesin upon three monosynaptic pathways of the cat. J. Pharmacol. & Exper. Therap., **118:** 309–317, 1956.
172. Leinasser, J. M. Contact dermatitis due to chlorpromazine. Northwest Med., **55:** 661–662, 1956.
173. Lemere, F. Habit-forming properties of meprobamate. A. M. A. Arch. Neurol. & Psychiat., **76:** 205–206, 1956.
174. Lemere, F. Drug habituation. J. A. M. A., **160:** 1431, 1956.
175. Lemere, F. New steroid hormone tranquilizing agent (Cetadiol). Am. J. Psychiat., **113:** 930, 1957.
176. Lesse, H., Heath, R. G., Mickle, W. A., Monroe, R. R. and Miller, W. H. Rhinencephalic activity during thought. J. Nerv. & Ment. Dis., **122:** 433–440, 1955.
177. Lesse, H. Electrographic recordings of amygdaloid activity during a conditioned response. Fed. Proc., **16:** 79, 1957.
178. Lessin, A. W. and Parkes, M. W. The relation between sedation and body temperature in the mouse. Brit. J. Pharmacol., **12:** 245–250, 1957.
179. Levine, J., Rinkel, M. and Greenblatt, M. Psychological and physiological effects of intravenous Pervitin. Am. J. Psychiat., **105:** 429–434, 1948–1949.
180. Levis, S., Preat, S., Beersaerts, J., Dauby, J., Beelen, L. and Bauginet, V. Pharmacological study on Hydroxyzine, V.C.B.-492; a disubstituted piperazine derivative. Arch. internat. pharmacodyn., **109:** 127–142, 1957.
181. Lim, R. K. S., Pindell, M. H., Glass, H. G. and Rink, K. The experimental evaluation of sedative agents in animals. Ann. New York Acad. Sc., **64:** 667–678, 1956.
182. Longo, V. G., von Berger, G. B. and Bovet, D. J. Action of nicotine and of the *ganglioplegiques centraux* on the electrical activity of the brain. J. Pharmacol. & Exper. Therap., **111:** 349–359, 1954.
183. MacLean, P. D., Horwitz, N. H. and Robinson, F. Olfactory-like responses in pyriform area to non-olfactory stimulation. Yale J. Biol. & Med., **25:** 159–172, 1952–1953.
184. Madi, M. L. and Kovitz, B. Experiences with methyl-phenidylacetate hydrochloride (Ritalin) in psychotic patients. Antibiotic Med., **3:** 309–311, 1956.
185. Magee, W. L., Berry, J. F. and Rossiter, R. J. Effect of chlorpromazine and azacyclonol on the labeling of phosphatides in brain slices. Biochim. et biophys. acta, **21:** 408–409, 1956.
186. Magee, W. L., Pritchard, E. T. and Strickland, K. P. Chlorpromazine and azacyclonol and the *in vitro* labeling of phosphatides in brain preparations. Fed. Proc., **16:** 215–216, 1957.
187. Malitz, S. and Hoch, P. H. Preliminary evaluation of a new phenothiazine derivative, NP-207. Psychiat. Quar., **30:** 633–646, 1956.
188. Malitz, S., Hoch, P. H. and Lesse, S. A two-year evaluation of chlorpromazine in clinical research and practice. Am. J. Psychiat., **113:** 540–545, 1956.
189. Manger, W. M., Schwarz, B. E., Baars, C. W., Wakim, K. G., Bollman, J. L., Petersen, M. C. and Berhson, J. Plasma and cerebrospinal fluid concentrations of epinephrine and norepinephrine in certain psychiatric conditions. Proc. XX Internat. Physiol. Cong., Brussels, 1956, pp. 610–611.
190. Marchini, E. and Valducci, A. Electroencephalographic observations on a new rapid-acting stimulant: Ritalin. Riv. neurol., **26:** 378–383, 1956.
191. Margolis, L. H. Pharmacotherapy in psychiatry. A review. Ann. New York Acad. Sc., **66:** 698–718, 1957.
192. Marrazzi, A. S. and Hart, E. R. Relationship of hallucinogens to adrenergic cerebral neurohumors. Science, **121:** 365–367, 1955.
193. Marrazzi, A. S. The effects of certain drugs on cerebral synapses. Ann. New York Acad. Sc., **66:** 496–507, 1957.
194. Martelli, G. The effects of reserpine therapy on the EEG of mental patients. Gior. psichiat. e neuropat., **84:** 323–325, 1956.
195. Martin, W. R. and Riehl, J. L. Quantitative comparison of the effects of chlorpromazine and pentobarbital on some autonomic responses. J. Pharmacol. & Exper Therap., **116:** 41–42, 1956.
196. Mattingly, T. W. and Sjoerdsma, A. The cardiovascular manifestations of functioning carcinoid tumors. Mod. Concepts Cardiovas. Dis., **25:** 337–341, 1956.
197. Mauceri, J. and Strauss, H. Effects of chlorpromazine on the electroencephalogram with report of a case of chlorpromazine intoxication. Electroencephalog. & Clin. Neurophysiol., **8:** 671–675, 1956.

198. Maxwell, R. A., Ross, S. D., Plummer, A. J. and Sigg, E. B. A peripheral action of reserpine. J. Pharmacol. & Exper. Therap., **119:** 69–77, 1957.

199. Maxwell, R. A., Plummer, A. J., Ross, S. D., Paytas, J. J. and Dennis, A. D. Arch. internat. Pharmacodyn., in press.

200. Mayer, S. W., Kelly, F. H. and Morton, M. E. The direct antithyroid action of reserpine, chlorpromazine and other drugs. J. Pharmacol. & Exper. Therap., **117:** 197–201, 1956.

201. Meier, R., Gross, F. and Tripod, J. Ritalin, a new synthetic compound with specific analeptic components. Klin. Wchnschr., **32:** 445–450, 1954.

202. Menguy, R. B., Bollman, J. L., Grindlay, J. H. and Cain, J. B. Biliary stasis produced by chlorpromazine. An experimental study. Proc. Staff Meet. Mayo Clin., **30:** 601–606, 1955.

203. Monnier, M. and Gangloff, H. Action of chlorpromazine, reserpine and serotonin on the unanesthetized rabbit's brain (cortex, diencephalon, rhinencephalon, and reticular formation). Electroencephalog. & Clin. Neurophysiol., **8:** 700, 1956.

204. Monroe, R. R., Heath, R. G., Mickle, W. A. and Llewellyn, R. C. Correlation of rhinencephalic electrograms with behavior. A study on humans under the influence of LSD and mescaline. Electroencephalog. & Clin. Neurophysiol., **9:** 623–642, 1957.

205. Moraczewski, A. S. and Dubois, K. P. Effect of chlorpromazine on oxygen consumption by tissue slices. Fed. Proc., **16:** 323–324, 1957.

206. Morison, R. S., Finley, K. H. and Lothrop, G. N. Influence of basal forebrain areas on the electrocorticogram. Am. J. Physiol., **139:** 410–416, 1942.

207. Moruzzi, G. and Magoun, H. W. Brain stem reticular formation and activation of the EEG. Electroencephalog. & Clin. Neurophysiol., **1:** 455–473, 1949.

208. Moyer, J. H. The pharmacology of chlorpromazine. Internat. Rec. Med., **168:** 301–311, 1955.

208a. Moyer, J. H., Kinross-Wright, V. and Finney, R. M. Chlorpromazine as a therapeutic agent in clinical medicine. A. M. A. Arch. Int. Med., **95:** 202–218, 1955.

209. Odland, T. M. Azacyclonol (Frenquel) hydrochloride in the treatment of chronic schizophrenia. J. A. M. A., **165:** 333, 1957.

210. Owen, J. E. and Verhave, T. The tranquilizing activity of some phenyl substituted cyclic amines. Proc. Am. Soc. Pharmacol. & Exper. Therap. Meeting, Johns Hopkins University, September, 1957.

211. Paasonen, M. K., MacLean, P. D. and Giarman, N. J. 5-hydroxytryptamine (serotonin, enteramine) content of structures of the limbic system. J. Neurochem., **1:** 326–333, 1957.

212. Palmer, D. M. Scalp EEG's of patients receiving oral benactyzine. Electroencephalog. & Clin. Neurophysiol., **9:** 716–719, 1957.

213. Papez, J. W. A proposed mechanism of emotion. A. M. A. Arch. Neurol. & Psychiat., **38:** 725–743, 1937.

214. Pelner, L. and Waldman, S. Chlorpromazine-induced jaundice. Postgrad. Med., **18:** 349–353, 1955.

215. Pennington, V. M. Cited by Berger, F. M. Meprobamate. Its pharmacologic properties and clinical usage. Internat. Rec. Med., **169:** 184–196, 1956.

216. Perlstein, M. A. Use of meprobamate (Miltown) in convulsive and related disorders. J. A. M. A., **161:** 1040–1043, 1956.

217. Peruzzo, L. and Forni, R. B. Action of chlorpromazine (Largactil) on tissue respiration (oxygen consumption). Presse méd., **61:** 1463, 1953.

218. Pfeiffer, C. C., Jenny, E. H. and Marshall, W. H. Experimental seizures in man and animals with acute pyridoxine deficiency produced by hydrazides. Electroencephalog. & Clin. Neurophysiol., **8:** 307–315, 1956.

219. Pfeiffer, C. C., Jenny, E. H., Gallagher, W., Smith, R. P., Bevan, W., Killam, K. F., Killam, E. K. and Blackmore, W. Stimulant effect of 2-dimethylaminoethanol. Science, **126:** 610–611, 1957.

220. Pfeiffer, C. C., Riopelle, A. J., Smith, R. P., Jenny, E. H. and Williams, H. L. Comparative study of the effect of meprobamate on the conditioned response, on strychnine and pentylenetetrazol thresholds, on the normal electroencephalogram, and on polysynaptic reflexes. Ann. New York Acad. Sc., **67:** 734–745, 1957.

221. Piala, J. J., High, J. P., Greenspan, K. and Burke, J. C. Further laboratory observations on 10-(3-dimethylaminopropyl)-2-(trifluromethyl)-phenothiazine hydrochloride (MC-4703). J. Pharmacol. & Exper. Therap., **119:** 176–177, 1957.

222. Pletscher, A., Shore, P. A. and Brodie, B. B. Serotonin as a mediator of reserpine action in brain. J. Pharmacol. & Exper. Therap., **116:** 84–89, 1956.

223. Pletscher, A. Release of 5-hydroxytryptamine by benzoquinolizine derivatives with sedative action. Science, **126:** 507, 1957.

224. Pokorny, C., Wilkinson, P. N., McCusker, E. N. and Hellwig, C. A. An effect of *Rauwolfia* alkaloids on the thyroid. Growth, **21:** 89, 1957.

225. Pollack, B. Recurrent thorazine-induced agranulocytosis. Am. J. Psychiat., **113:** 557–558, 1956.

226. Preston, J. B. Effects of chlorpromazine on the central nervous system of the cat. A possible neural basis for action. J. Pharmacol. & Exper. Therap., **118:** 100–115, 1956.

227. Pribram, K. H. and Kruger, L. Functions of the "olfactory brain." Ann. New York Acad. Sc., **58:** 109–138, 1954.

228. Rashkis, H. A. and Smarr, E. R. Psychopharmacotherapeutic research. A. M. A. Arch. Neurol. & Psychiat., **77:** 202–209, 1957.

229. Rau, G. C., Auyong, T., Paradise, R. R., Baumgardt, J. P. and Eisenbrandt, L. L. Effect of chlorpromazine hydrochloride on oxygen uptake of rat brain slices. J. Pharmacol. & Exper. Therap., **116:** 48, 1956.

230. Raymond, M. J. and Lucas, C. J. Benactyzine in psychoneurosis. With a note on the EEG changes in normal subjects. Brit. M. J., **1:** 952–954, 1956.

231. Reilly, J. and Regan, P. F., IIIrd. Plasma catechol amines in psychiatric patients. Proc. Soc. Exper. Biol. & Med., **95:** 377–380, 1957.

232. Rider, J. A. Effect of prolonged oral administration of reserpine (Reserpoid) on gastric secretion. Proc. Soc. Exper. Biol. & Med., **90:** 636–638, 1955.

233. Rider, J. A., Meikle, M., Agcaoili, L. F. and Deroin, J. Effects of chlorpromazine on physical properties of bile. Fed. Proc., **16:** 330, 1956.

234. Riley, R. F. and Berger, F. M. Metabolism of Myanesin (3-(*o*-toloxy)-1,2-propanediol). Arch. Biochem., **20:** 159–160, 1949.

235. Rinaldi, F. and Himwich, H. E. Frenquel corrects certain cerebral electrographic changes. Science, **122:** 198–199, 1955.

236. Rinaldi, F. and Himwich, H. E. A comparison of effects of reserpine and some barbiturates on the electrical activity of cortical and subcortical structures of the brain of rabbits. Ann. New York Acad. Sc., **61:** 27–35, 1955.

237. Rinaldi, F. and Himwich, H. E. Drugs affecting psychotic behavior and the function of the mesodiencephalic activating system. Dis. Nerv. System, **16:** 133–141, 1955.

238. Robbins, E. B. and Miller, J. A. Inhibition of analgesia by butamoxane derivatives. Proc. Am. Soc. Pharmacol. & Exper. Therap., Baltimore, September, 1957, to be published.

239. Robinson, H. M., Robinson, R. C. V. and Strahan, J. F. Hydroxyzine (Atarax) hydrochloride in dermatological therapy. J. A. M. A., **161:** 604–606, 1956.

240. Rodin, E. A., De Jong, R. N., Waggoner, R. W. and Bagchi, B. K. Relationship between certain forms of psychomotor epilepsy and "schizophrenia." A. M. A. Arch. Neurol. & Psychiat., **77:** 449–463, 1957.

241. Rosner, B. S., Fierman, L. B. and Kramer, J. F. Clinical evaluation of Meratran and Frenquel on a chronic psychotic population. Am. J. Psychiat., **113:** 993, 1957.

242. Rothballer, A. B. Studies on the adrenaline-sensitive component of the reticular activating system. Electroencephalog. & Clin. Neurophysiol., **8:** 603–621, 1956.

243. Rothlin, E. Lysergic acid diethylamide and related substances. Ann. New York Acad. Sc., **66:** 668–676, 1957.

244. Rotstein, J., Frick, P. S. and Schiele, B. C. Agranulocytosis associated with chlorpromazine therapy. A. M. A. Arch. Int. Med., **96:** 781–786, 1955.

245. Rudy, L. H., Himwich, H. E. and Tasher, D. C. Clinical evaluation of two phenothiazine compounds promazine and mepazine. Am. J. Psychiat., **113:** 979–983, 1957.

246. Ryall, R. W. Some actions of chlorpromazine. Brit. J. Pharmacol., **11:** 339–345, 1956.

247. Saunders, J. C., Radinger, N. and Kline, N. S. A theoretical and clinical approach to treating depressed and regressed patients with Iproniazid. To be published.

248. Schneider, J. A., Plummer, A. J., Earl, A. E. and Gaunt, R. Neuropharmacological aspects of reserpine. Ann. New York Acad. Sc., **61:** 17–26, 1955.

249. Schneider, J. A. Further characterization of central effects of reserpine (Serpasil). Am. J. Physiol., **181:** 64–68, 1955.

250. Schut, J. W. and Himwich, H. E. The effect of Meratran on 25 institutionalized mental patients. Am. J. Psychiat., **111:** 837–840, 1955.

251. Schwarz, B. E., Wakim, K. G., Bickford, R. G. and Lichtenheld, F. R. Behavioral and electroencephalographic effects of hallucinogenic drugs. A. M. A. Arch. Neurol. & Psychiat., **75:** 83–90, 1956.

252. Seifter, J., Glassman, J. M. and Ruazzino, F. Pharmacological properties of promazine. J. Pharmacol. & Exper. Therap., **119:** 183, 1957.

253. Selling, L. S. Clinical study of a new tranquilizing drug. Use of Miltown (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate). J. A. M. A., **157:** 1594–1596, 1955.

254. Selling, L. S. A clinical study of Miltown, a new tranquilizing agent. J. Clin. & Exper. Psychopath., **17:** 7–14, 1956.

255. Sem-Jacobsen, C. W. Depth electroencephalographic studies of the activity in the human brain and the effect of some drugs (including mescaline, LSD-25 and chlorpromazine). Electroencephalog. & Clin. Neurophysiol., **8:** 717, 1956.

256. Seneca, H. Hydroxyzine (Atarax) as a therapeutic agent. Antibiotic Med., **4:** 25–30, 1957.

257. Shalowitz, M. Hydroxyzine. A new therapeutic agent for senile anxiety states. Geriatrics, **11:** 312–315, 1956.

258. Shaw, E. N. and Woolley, D. W. Pharmacological properties of some antimetabolites of serotonin having unusually high activity on isolated tissues. J. Pharmacol. & Exper. Therap., **111:** 43–53, 1954.

259. Shay, H. and Siplet, H. Study of chlorpromazine jaundice, its mechanism and prevention. Gastroenterology, **32:** 571–591, 1957.

260. Shealy, C. N. and Peele, T. L. Studies on amygdaloid nucleus of the cat. J. Neurophysiol., **20:** 125–139, 1957.

261. Shore, P. A., Silver, S. L. and Brodie, B. B. Interaction of reserpine, serotonin and lysergic acid diethylamide in brain. Science, **122:** 284–285, 1955.

262. Shore, P. A., Silver, S. L. and Brodie, B. B. Interaction of serotonin and lysergic acid diethylamid (LSD) in the central nervous system. Experientia, **11:** 272–273, 1955.

263. Shore, P. A., Mead, J. A. R., Kuntzman, R. G., Spector, S. and Brodie, B. B. On the physiological significance of monoamine oxidase in brain. Science, **126:** 1063–1064, 1957.

264. Shore, P. A., Olin, J. S. and Brodie, B. B. Release of brain norepinephrine by reserpine. Fed. Proc., **16:** 335–336, 1957.

265. Shore, P. A., Pletscher, A., Tomic, E. G., Carlsson, A., Kuntzman, R. and Brodie, B. B. Role of brain serotonin in reserpine action. Ann. New York Acad. Sc., **66:** 609–617, 1957.

266. Shore, P. A. and Brodie, B. B. LSD-like effects by reserpine in rabbits pretreated with Iproniazid. Proc. Exper. Biol. & Med., **94:** 433–435, 1957.

267. Sigg, E. B. and Schneider, J. A. Mechanisms involved in the interaction of various central stimulants and reserpine. Electroencephalog. & Clin. Neurophysiol., **9:** 419–427, 1957.

268. Simon, J. L. and Taube, H. A preliminary study on the use of methedrine in psychiatric diagnosis. J. Nerv. & Ment. Dis., **104:** 593–598, 1946.

269. Sjoerdsma, A., Smith, T. E., Stevenson, T. D. and Udenfriend, S. Metabolism of 5-hydroxytryptamine (serotonin) by monoamine oxidase. Proc. Soc. Exper. Biol. & Med., **89:** 36–38, 1955.

270. Slater, I. H., Jones, G. T. and Young, W. K. Mode of action of phenaglycodol, a new neurosedative agent. Proc. Soc. Exper. Biol. & Med., **93:** 528–531, 1956.

271. Slater, I. H. and Jones, G. T. Pharmacologic properties of Butamoxane and related compounds. Proc. Am. Soc. Pharmacol. & Exper. Therap., Baltimore, September, 1957, to be published.

272. Smith, R. P., Wagman, A. I. and Riopelle, A. J. Effects of reserpine on conditioned avoidance behavior in normal and brain-operated monkeys. J. Pharmacol. & Exper. Therap., **117:** 136–141, 1956.

273. Straker, M. Intravenous Methamphetamine —adjuvant to psychotherapy. Am. J. Psychiat., **109:** 853–855, 1952–1953.

274. Sulkowitch, H., Perrin, G. M. and Altschule, M. D. Excretion of urinary "epinephrines" in psychiatric disorders. Proc. Soc. Exper. Biol. & Med., **95:** 245–247, 1957.

275. Sulman, F. G. and Winnik, H. Z. Hormonal depression due to treatment of animals with chlorpromazine. Nature, London, **178:** 365, 1956.

276. Swinyard, E. A., Chin, L. and Fingl, E. Withdrawal hyperexcitability following chronic administration of meprobamate to mice. Science, **125:** 739–740, 1957.

277. Taketoma, Y., Shore, P. A., Tomich, E. G., Kuntzman, R. and Brodie, B. Studies on the mechanism of reserpine-induced epinephrine release and hyperglycemia. J. Pharmacol. & Exper. Therap., **119:** 188, 1957.

278. Terzian, H. Electroencephalographic study of the central action of Largactil. Rass. neurol. vegetat., **4:** 211–215, 1952.

279. Terzian, H. Study of the action of Largactil and Pendiomide on the electrical activity of the rabbit brain. Rev. neur., Paris, **91:** 445–453, 1954.

280. Tuchmann-Duplessis, H. The influence of reserpine on the endocrine glands. Presse méd., **64:** 2189–2192, 1956.

281. Tucker, K. and Wilensky, H. A clinical evaluation of meprobamate therapy in a chronic schizophrenic population. Am. J. Psychiat., **113:** 698–703, 1957.

282. Udenfriend, S., Weissbach, H. and Bogdanski, D. F. Biochemical findings relating to the action of serotonin. Ann. New York Acad. Sc., **66:** 602–608, 1957.

283. Ulett, G. A. Preliminary observations on convulsive and subconvulsive treatments induced by intermittent photic stimulation. Am. J. Psychiat., **109:** 741–748, 1952–1953.

284. Unna, K. R. A review of the neurophysiological effects of psychotherapeutic drugs. Ann. New York Acad. Sc., **66:** 777–783, 1957.

285. Verhave, T. and Fadley, D. Some preliminary observations concerning the behavioral effects of Butamoxane and related compounds. Proc. Am. Soc. Pharmacol. & Exper. Therap., Baltimore, September, 1957, to be published.

286. Waalkes, T. P. and Weissbach, H. *In vivo* release of histamine from rabbit blood by reserpine. Proc. Soc. Exper. Biol. & Med., **93:** 394–396, 1956.

287. Wase, A. W., Christensen, J. and Polley, E. The accumulation of S^{35} chlorpromazine in brain. A. M. A. Arch. Neurol. & Psychiat., **75:** 54–56, 1956.

288. Weiskrantz, L. and Wilson, W. A. The effects of reserpine on emotional behavior of normal and brain-operated monkeys. Ann. New York Acad. Sc., **61:** 36–55, 1955.

289. Weissbach, H., Bogdanski, D. F., Redfield, B. G. and Udenfriend, S. Studies on the effect of vitamin B_6 on 5-hydroxytryptamine